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CURRENT RESEARCH TOWARD A GLOBAL CONTROL OF MALARIA*

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AN immense volume of research on malaria has been carried out in recent years. It has covered a wide field, and has included studies on the parasitology, epidemiology and chemotherapy of the disease, mosquito bionomics and the development of antimalarial drugs, insecticides and repellents. Valuable information has been obtained in the course of malaria therapy of nervous disorders and by investigations of the malaria of birds, monkeys and rodents. All these activities have an important bearing on the planning of control measures, although the part played by some of them is at first sight less obvious than that of others.

In certain instances, to make the story of recent researches in this field more intelligible and more interesting, I propose to give some account of earlier investigations that led up to them.

RESEARCHES ON THE LIFE CYCLE OF THE MALARIA PARASITE

From the standpoint of malaria control, the importance of this work lies in its relation to the development of antimalarial drugs.

The parasite of human malaria was discovered in the blood of a patient in a military hospital in Algeria by the French army surgeon, Alphonse Laveran, in 1880, but it was not until 1897 that Ronald Ross, in India, observed pigmented oocysts on the stomach wall of a mosquito that had fed on a malaria patient. In the same year MacCallum, as the result of studies begun while he was an undergraduate at Johns Hopkins, showed, by his observations on exflagellation, that malaria parasites have a sexual, as well as an asexual, phase of development. In 1898 Ross worked out the entire life cycle of a plasmodium of bird malaria, and in the light of his previous observation of human parasites in the stomach of a mosquito, forecast that the sexual phase of the latter would prove to be of the same character. This prediction was fulfilled a few months later by the work of the Italian observers Grassi, Bignami and Bastianelli.

Confirmation of the mosquito transmission of malaria was furnished by two experiments planned by Sir Patrick Manson in 1900. Three men, Low, Sambon and Terzi, lived in a screened hut in an intensely malarious section of the Roman Campagna throughout the season of malaria transmission, and none of them contracted the disease. Meanwhile, a batch of mosquitoes that had fed on malaria patients in Rome were sent to London and there allowed to bite two persons (one of them Manson's son), who had never before been exposed to malarial infection. Both of these volunteers had typical attacks of malaria after a normal incubation period.

Thus, more than fifty years ago, the mode of transmission of malaria had been proved, and the existence of an asexual phase in man and a sexual phase in the mosquito had been demonstrated. The latter had been followed out in full, but about the former one question still remained unanswered: What happens to the parasite during the period between the injection of sporozoites into the body and the first demonstrable appearance of asexual forms in the peripheral blood?

Schaudinn, in 1903, reported that he had seen the sporozoite actually penetrating a red blood cell, and this finding was at first generally accepted. But as the years went by, and no one was able to repeat this observation despite the most intensive search, it gradually became evident that Schaudinn had been mistaken and that the parasite must undergo another phase of development during the prepatent period, as indeed had been suspected by Grassi as early as 1900.

Raffaele, who described unpigmented parasites in avian malaria in 1934, was the first to recognize that these represented a definite phase of development in the tissues, as distinct from that occurring in the blood. James and Tate, in 1937, described the exo-erythrocytic schizogony of *Plasmodium gallinaceum* in the brain capillaries of the fowl, but the mystery of what happens during the period immediately after infection remained for a while unsolved.

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In 1940, however, Shortt and his colleagues in India, and Mudrow in Germany, independently observed pre-erythrocytic forms of avian malaria during the prepatent period. This work was amplified by that of Huff and Coulston (1944), who described in detail the complete development of the pre-erythocytic states of *P. gallinaceum*.

During the period 1945–47, Fairley, in Australia, carried out some highly significant studies on human malaria, by which it was shown that after infection by mosquito bites the sporozoites circulate in the blood for about half an hour, after which they disappear. This was proved by the inoculation into volunteers of large quantities of blood, which produced malaria in the recipients if drawn from the donor within half an hour of infection, but were subsequently innocuous for six days after inoculation with *P. falciparum* and nine days after that with *P. vivax*.

At this time Shortt and his colleagues at the London School of Hygiene had just begun the classic series of researches on mammalian malaria that were destined to have such far-reaching results. In 1948, after massive infection by the bites of several hundreds of heavily infected mosquitoes, which were afterward ground up and injected parenterally into a monkey, pre-erythrocytic forms of *P. cynomolgi* were observed in a section of liver removed seven days later.

Subsequently, less mature stages of the parasite were found in other monkeys similarly infected, the earliest to date being in sections excised on the second day. It has also been proved that in monkey malaria exo-erythrocytic parasites can persist in the liver after the blood infection has been established. These forms are thought to be responsible for the phenomenon of relapse.

The demonstration of the tissue phase of *P. cynomolgi* in the monkey made it practically certain that a similar phase exists in human malaria, and this was soon established for both *P. vivax* and *P. falciparum*. This work was carried out by Shortt and his team at the London School of Hygiene, in collaboration with the staff of the Medical Research Council's Malaria Laboratory at Horton Hospital.

The vivax experiment was particularly interesting, because in addition to proving the existence of a tissue phase in the liver in human malaria, it shed considerable light on the mechanism of malarial immunity. The subject of the experiment had undergone malaria therapy by means of the same strain of *P. vivax*, two years previously, and had experienced some 13 peaks of fever before the attack was terminated. For the experiment, he was subjected to the bites of over 2000 heavily infected mosquitoes, and was also given an emulsion of the salivary glands of 200 mosquitoes from the same batch intravenously.

This was certainly the largest dose of sporozoites that had ever been injected into a human being. The experiment was successful, in that pre-erythrocytic forms of the parasite were found in sections from a piece of liver removed by open operation seven days after infection; but although the volunteer was under observation for the next eighteen months, no parasites were ever found in the peripheral blood, nor did he experience any clinical sign of malaria beyond a slight transient rise of temperature on the fifteenth day. This demonstrates not only the extraordinary solidity of the immunity conferred by a previous infection with the same strain of parasite but also the fact that the immunity response in malaria is directed primarily against the parasites in the blood, which are destroyed as soon as they enter it; whereas the pre-erythrocytic forms in the liver are apparently unaffected.

The falciparum experiment, which was equally successful, had one curious sequel. Some months later, the subject suffered from a duodenal ulcer, which perforated. The surgeon who operated upon him in this emergency stated that his life had probably been saved by reason of the previous operation on his liver. This had left certain adhesions, which sealed off the site of perforation from the rest of the abdominal cavity and so prevented a general peritonitis. The patient made a perfect recovery, and thus reaped a fitting reward for his previous contribution to the advance of scientific knowledge.

The existence of a pre-erythrocytic phase in *P. falciparum* has recently been confirmed by the work of Martin Young and his colleagues at the Laboratory of Tropical Diseases, Columbia, South Carolina.

Research on the Development of Antimalarial Drugs

Before the outbreak of World War I the only specific antimalarial drugs known were the cinchona alkaloids, of which the most commonly used was quinine.

Cinchona bark was introduced into Europe from South America by the Spaniards in 1640. During the latter half of the eighteenth century the bark was extensively used in India, where it was popularized by the surgeons of the numerous ships trading with that country. During the first half of the nineteenth century cinchona passed through a phase of unpopularity that was largely due to the malign influence of a certain Dr. Johnson, who visited Calcutta in 1804. He treated his first case with cinchona and failed to effect a cure. He bled his second patient, who recovered, and thenceforth adopted a line of treatment consisting of mercury in large doses, purging and venesection. After a brief sojourn in India he returned to London and wrote a book on tropical diseases in which the administration of cinchona bark as a remedy for malaria was vehemently condemned. As a result,

the use of the bark was practically abandoned in India, and even when reintroduced it was for many years used merely as a tonic after the subsidence of the fever. The treatment consists mainly of bleeding (1000 cc., 20 leeches, on the first day, 600 cc. on the second, 720 cc., 12 leeches, on the third and 720 cc., 8 leeches on the fourth), quinine being given in a dosage of 0.03 gm., repeated after an hour, on the fifth day; in addition, during this period, the patient received 3.5 gm. of calomel, 3.06 gm. of blue pill and daily purges of colocynth, hyoscyamus, jalap, camboge, senna and salts. In contrast was the excessively heavy quinine dosage employed among British troops in Macedonia in 1916: 2 gm. orally and 2 gm. intramuscularly every day for twelve days, 4 gm. orally for the next three days and 1.2 gm. orally for the next fourteen days — 70.8 gm. in twenty-nine days.

Quinine has a powerful action on the erythrocytic forms of most strains of malaria parasites, and it is doubtful whether any of the synthetic drugs now employed for the treatment and prophylaxis of the disease would ever have been evolved had the two world wars never occurred. The fact that the Germans were deprived of all sources of quinine during World War I inspired the search for synthetic antimalarials that resulted in the production first of pamaquine (plasmochin) in 1926, and later of mepacrine (quinacrine) in 1931. The Germans went on to synthesize two other compounds, chloroquine (resochin) and sontoquine (sontochin), and both these were undergoing field trials when World War II broke out in 1939.

In World War II the Allies in their turn were cut off from all sources of quinine, and an enormous volume of research on synthetic antimalarial drugs was undertaken on both sides of the Atlantic. The greater part of this work was carried out in the United States, where more than 14,000 substances were tested against avian malaria, and about 100, selected from 20 different chemical groups, on human beings. In the course of these investigations the properties of mepacrine were explored in detail, chloroquine was shown to be the most powerful schizonticide yet produced, a modification of chloroquine called amodiaquine (camoquin) was evolved, and the 8-aminoquinoline group was explored with the object of finding a less toxic and more effective drug than pamaquin for the prevention of relapse. This last-named work resulted in the production of pentaquine and isopentaquine and finally primaquine, which is claimed to be less toxic and more effective than either.

Meanwhile, British chemists, working on a smaller scale, extended and confirmed knowledge of existing drugs, and pursued a search for new ones, which led to the evolution of an entirely new type of compound, proguanil (chlorguanide, Paludrine). More recently another new drug has been produced under the name of pyrimethamine (daraprim), and this is now undergoing extensive field trials.

The evolution of the first synthetic antimalarial compounds from methylene blue to mepacrine and later to chloroquine and amodiaquine makes an interesting story.

The Germans thought that methylene blue might have an action on the malaria parasite because it stains and therefore must enter it. Investigations on this and allied compounds led to the production of a substance that proved to have some action in avian malaria. The important difference between this substance and methylene blue was the presence in the former of a basic side chain. The Germans now introduced basic side chains of various kinds into the quinolene nucleus because this nucleus is present in quinine, and eventually they synthesized pamaquine.[4]

Pamaquine is very active in avian malaria, but its effect on human malaria proved in many ways disappointing, and the Germans therefore pursued their search for a more satisfactory drug. They put the basic side chain that they had evolved for pamaquine into other heterocyclic nuclei, and finally produced mepacrine, in which the side chain is opposite the ring nitrogen, as in quinine.

Chloroquine was evolved by removal of the right-hand ring of mepacrine, and sontochin, with its extra CH_3 group, was later prepared because in its early trials chloroquine was thought to have unpleasant side effects. Amodiaquine is a further variation of chloroquine.

Proguanil was produced as the result of researches into certain pyrimidine substances that were found to have some antimalarial activity. The subsequent development of this work led to an investigation of the biguanides, the group to which proguanil belongs. The workers concerned have admitted that there was an element of luck in the discovery of this drug, as indeed frequently happens in research work but is not always so frankly acknowledged.

Pyrimethamine had its origin in studies concerned primarily with antagonists related to the heterocyclic constituents of the nucleic acids. It is one of the group of 2:4-diaminopyrimidines, all of which are competitive antagonists of folic and folinic acids in the growth of *Lactobacillus casei*. The formal structural analogy between the diaminopyrimidines and proguanil, together with certain similarities in microbiologic behavior, suggested that they should be tried as antimalarial drugs. Recently, it has been shown that the active form of proguanil is a metabolite, which bears a striking resemblance to pyrimethamine. What was originally proposed as a purely formal analogy, therefore, is now regarded as a true structural analogy.

To understand the mode of action of antimalarial drugs, it is necessary to consider them in relation to the various phases of the life cycle of the malaria

parasite in the human body. Although recent researches on the life cycle of the parasite have shed new light on the action of antimalarial drugs, chemotherapeutic studies have also provided a notable stimulus to work on the life cycle of the parasite, by providing circumstantial evidence of the existence of an exo-erythrocytic phase.

In theory, a drug may act on the malaria parasite in five possible ways (Table 1): against the sporozoites when they first enter the human body: against the primary tissue, or pre-erythrocytic phase; against the asexual parasites in their erythrocytic phase; against the sexual parasites in their erythrocytic phase; and against the late exo-erythrocytic or secondary tissue phase, to which the phenomena of latency and late relapse in vivax malaria have been attributed.

TABLE 1. *Mode of Action of Antimalarial Drugs.*

CLASS OF DRUG	PRIMARY TISSUE PHASE	ERYTHROCYTIC PHASE		SECONDARY TISSUE PHASE	MOSQUITO PHASE
		ASEXUAL FORMS	SEXUAL FORMS		
Cinchona alkaloids — quinine, etc.	—	Effective action	—	—	—
9-Aminoacridines — mepacrine, etc.	—	Effective action	—	—	—
4-Aminoquinolines — chloroquine, camoquin, etc.	—	Effective action	—	—	—
8-Aminoquinolines — pamaquine, primaquine, etc.	Not effective for this purpose*	Not effective for this purpose*	Effective action	Effective action	—
Biguanides — proguanil (Paludrine), etc.	Effective action†	Action too slow for treatment of clinical attack	—	—	Effective action
2:4-diaminopyrimidines-pyrimethamine (daprim), etc.	Effective action†	Action too slow for treatment of clinical attack	—	—	Effective action

*Except in dangerously high dosage.
†Fully effective for this purpose only in falciparum malaria.

The classes of antimalarial drugs in common use are the cinchona alkaloids (quinine, totaquina); the 9-aminoacridines (mepacrine); the 4-aminoquinolines (chloroquine, amodiaquine); the 8-aminoquinolines (pamaquine, primaquine); and the 2:4-diaminopyrimidines (pyrimethamine).

No drug as yet tested has any demonstrable effect on the sporozoite stage of the malaria parasite. The cinchona alkaloids, the aminoacridines, the 4-aminoquinolines, the biguanides and the diaminopyrimidines have a destructive action on the asexual forms of all four species of human malaria parasite in the erythrocytic phase, though the action of the last two is generally too slow for treatment of the clinical attack. The 8-aminoquinolines do not affect the asexual parasites in the erythrocytic phase, but have a powerful, destructive action on the gametocytes. They also act on the secondary exo-erythrocytic forms of *P. vivax*. They have an inhibitory effect on the pre-erythrocytic forms of both *P. falciparum* and *P. vivax*, but only when employed in dosage too high for routine use.

The biguanides and the diaminopyrimidines are the only classes of drugs that can be used with safety against the pre-erythrocytic phase, and so far as is known they are effective only in falciparum infections. They have no action on the sexual forms of *P. falciparum* in the peripheral blood, but proguanil has been shown to render these forms incapable of completing their development in the mosquito. The diaminopyrimidines resemble the biguanides in many respects, and it is probable that they will be found to affect the mosquito phase of the parasite in the same way. Neither of these groups of drugs is suitable for treatment of the clinical attack, their chief value being in prophylaxis.

Of the drugs in use at present, quinine is now rarely employed except for the treatment of chronic relapsing vivax malaria in combination with pamaquine or primaquine, or for parenteral injection in cases of grave emergency. Mepacrine, the great standby in World War II, in which its use as a suppressant kept the Allied armies on their feet in southeast Asia and the Pacific at a time when the Japanese were gravely hampered by malarial casualties, has now been largely replaced by chloroquine and amodiaquine, which are used both for treatment of the clinical attack and for suppression.

Proguanil is extensively used by the British civil and military authorities for prophylaxis, and it has kept the malaria rate in Malaya at a low level during the difficult postwar years. Pyrimethamine, like proguanil, is not sufficiently rapid in action for treatment of the clinical attack, but promises to be of value in prophylaxis. It has recently been shown at Horton Hospital, England, that a single dose of 25 mg. of this drug administered once a week can afford complete protection against a West African strain of *P. falciparum*. Both these compounds have a tendency to produce drug resistance if used in subtherapeutic dosage, a disadvantage that has not yet been reported with chloroquine or amodiaquine.

The search for new antimalarial drugs goes on without ceasing, for none of those as yet tested possess the properties necessary to meet all requirements. The target aimed at is the production of a drug that in a single dose will resolve clinical symp-

toms and sterilize the infection without risk of toxic side effects and that can be manufactured in unlimited quantities at moderate cost.

It may be asked what part is played by drugs in the strategy of global control of malaria. In theory malaria could be eliminated in any area by administration to all inhabitants of a drug that would destroy the parasites in the blood. But attempts to control the disease among the general population by means of mass drug prophylaxis have hitherto invariably failed, chiefly because it is impossible to ensure the administration of any drug to persons who are not actually sick. This applies particularly to infants and young children, who represent an important reservoir of infection.

Mass drug prophylaxis is however a useful measure for populations under disciplinary control such as bodies of troops and labor forces employed in plantations or in the construction of large engineering projects. In such cases it is often convenient to administer the drug weekly at the time when the men receive their pay. It is also useful in malaria-eradication schemes in the event that indigenous cases arise as the result of infection imported from outside the zone under protection.

Researches on the Development of Insecticides

For a proper appreciation of this work it is necessary to cast one's mind back to the earlier attempts to control malaria by antimosquito measures. For the first twenty years of the present century attention was focussed almost exclusively on the destruction of the aquatic stages of mosquitoes by means of oil. About thirty years ago an arsenical preparation, Paris green, was introduced as a larvicide, and this, along with oil, continued to be used up to the outbreak of World War II. Paris green was largely instrumental in the eradication of *Anopheles gambiae* from Brazil in 1940 and from Egypt in 1944-45.

The hand swatting of anopheline mosquitoes in the quarters occupied by laborers was practiced by a sanitary inspector named Proctor in Panama as early as 1908, and is said to have been of considerable value in reducing the incidence of malaria. But the systematic destruction of adult mosquitoes by spraying of dwelling houses was not put into practice till about twenty years later, when Swellengrebel introduced it in Holland. The first use of this method in the tropics was in 1932 in South Africa, where it was applied in Zulu huts to combat a malaria epidemic, with excellent results. It was introduced into India in 1936, and was practiced extensively in that country up to the outbreak of World War II. The active agent in the spray used in all these campaigns was pyrethrum, which has a powerful immediate knockdown effect but no residual action. For this reason its application has to be repeated at frequent intervals, adding considerably to the expense of the method and to the disturbance of the householder.

Toward the close of the war the situation was completely revolutionized by the introduction of residual insecticides, whereby sprayed surfaces remained lethal to mosquitoes alighting on them for many weeks or even months. The first of these, DDT, was originally synthesized by a German scientist in 1874, but its remarkable properties as an insecticide were not recognized until twenty-five years later, when it was first used for the control of agricultural pests. In 1945 supplies became available for general use on a wide scale, and since then it has been applied on an ever-increasing scale in almost every country in the world where malaria is a serious public-health problem. It is estimated that at the present time about 100,000,000 people are under its protection.

At first the formula was a simple solution of DDT in kerosene, and this proved effective under certain conditions — for example, in British Guiana, where the houses are nearly all built of hardwood, and the chief mosquito vector, *A. darlingi*, is extremely domestic in its resting habits. But it was later found that on absorbent materials such as the dried mud used for house construction in many tropical countries, and particularly where the soil consists largely of red laterite, serious loss of the insecticide occurred through absorption. It was also found that emulsions of DDT were not absorbed to the same extent as kerosene solutions by mud and plaster surfaces, and that "wettable powders," which are powders treated with wetting agents to permit them to remain suspended in water sufficiently long to be sprayed, were still less liable to absorption. Most health authorities in various parts of the world now use wettable powders in suspension for large-scale work, supplemented by solutions in white kerosene for better-class houses where the greyish deposit caused by the suspension is an objection.

BHC (benzene hexachloride), discovered by Michael Faraday in 1825, although not recognized as an insecticide until 1942, has received less attention and less publicity than DDT, but has been found effective under certain conditions. It is more highly lethal to mosquitoes and to certain other insects than DDT, but its residual effect is less lasting, so that it must generally be applied more frequently. A disadvantage of the crude product is a somewhat unpleasant smell, but this is said to have been largely eliminated in the more recently evolved formulas.

A number of other residual insecticides are now on the market, the most promising of them being dieldrin, which is now undergoing extensive field trials. This product is said to combine the persistence of DDT with the high insecticidal toxicity of BHC.

When residual insecticides were first introduced and their remarkable powers were appreciated, it seemed as though the main problem of malaria

control was to all intents and purposes solved, and that future progress would be plain sailing. All that seemed necessary was the development of suitable apparatus for applying the spray and a plant adequate for producing it in sufficient quantity at an economical price. But, as is often true, the matter proved to be not so simple after all, and an immense volume of research has been expended during the last eight years. Many advances have been made, but there have been a number of unexpected setbacks, and much is still to be learned.

I have mentioned the variations in results obtained by the application of insecticides to different types of surface. It has further been demonstrated that crystal size is a matter of supreme importance. The essential requirement is a particle size of about 10 to 20 μ. Such small crystals are easily picked up on the feet and legs of insects, and though initial contact with the treated surface may be brief, enough of the crystals remain attached to the insect's hairy legs to ensure death.

If these small crystals can be surrounded by a film of oil, they are picked up still more readily, and if the film of oil contains the insecticide in solution the toxic effects are accelerated. Oil solutions are more toxic than any other formulas so long as they remain wet, but most oils used as solvents are volatile, and as they dry out after application the insecticide contained in them crystallizes into small particles, varying in size and shape according to the properties of the oil and of any additives, the rapidity of evaporation, the type of surface to which it is applied, and perhaps to other factors.

Thus, though on nonabsorbent surfaces oil solutions, while still wet, are the most toxic form of insecticide, they are usually unsuitable in that form since, to retain their activity, they must remain wet. When they dry out, their crystal form cannot be controlled, and they are often not of the most suitable size and shape for attachment to the legs of the insect. As I have already indicated, on absorbent surfaces, and particularly on dried mud, their surface deposits are so reduced by absorption that they are largely ineffective. Emulsions behave in much the same way as solutions, though there may be some that break down quickly enough to prevent serious loss by absorption.

The desired crystal form can be obtained for wettable powders or suspensions by grinding in suitable dust diluents such as those used for paint manufacture, but it is important that the particles of the diluent are of about the same size as those of the insecticide, and that the proportion of the diluent is not too high. In some cases, the diluent overshadows or covers the smaller or fewer insecticide particles, so that alighting mosquitoes do not make contact.

Wettable powders or suspensions are not usually suitable for nonabsorbent surfaces, since they contain wetting agents as well as diluents. These agents are absorbed with the water carrier when the suspensions are applied to absorbent surfaces such as mud, but they dry on nonabsorbent surfaces and stick the crystals of the insecticide down too tightly.

It has been mentioned that the crystal of insecticide has enhanced toxicity if it is surrounded by a film of oil. Suspensions in which this occurs have now been produced, and have proved more toxic in laboratory and field experiments than any other formula available.

In addition to the investigations on toxicity and physical structure of insecticides to which I have just referred, a great deal of research has been devoted to the development of suitable apparatus for their application. This is by no means an easy problem, for to obtain the optimum effect the insecticide must be applied evenly and without waste, the droplets sprayed must be of the required size, and the sprayer must be made of a metal that is not affected by the action of the spray.

It is also essential, particularly under tropical conditions, that the apparatus be as simple as possible, and not liable to get out of order easily when operated by unskilled laborers. It cannot be said that any of the sprayers as yet devised is entirely suitable, though considerable assistance has been given by the Expert Committee on Insecticides of the World Health Organization in drawing up specifications. The type found most generally useful for work in the tropics is a form of stirrup pump with an adjustable lance and a nozzle that gives a flat jet.

Another aspect of the problem to which much attention is now being paid is the intensive study of mosquito bionomics. It happened that in regions where the earliest large-scale residual spray campaigns were carried out — for example, in South America and southern India — the local malaria vector was in each case one whose resting habits were predominantly domestic. These campaigns were attended with such dramatic success that it was assumed in many quarters that global control of malaria was already in sight.

Subsequent experience with other vectors has in some cases been disappointing, and has emphasized the inadequacy of knowledge of the habits of the mosquitoes whose destruction is to be encompassed. These findings have stimulated more careful and detailed studies of the resting habits of the vector species both inside and outside buildings.

Certain species formerly not considered to be domestic in their habits are more likely to enter houses than had previously been thought to be so and others — for instance, *A. gambiae*, the chief vector throughout equatorial Africa — are not so domestic as previous studies had suggested. Knowledge of the bare fact that a certain species of mosquito enters houses to feed is not sufficient; it must

also be ascertained how long they remain there and exactly where they rest.

I mentioned above that certain antimalarial drugs had a tendency to produce resistant strains of malaria parasite. A similar bogey has been encountered in residual sprays, and this has proved an unexpected setback.

When these insecticides were first introduced they were everywhere hailed with enthusiasm by the local population, not so much because they killed mosquitoes as because they also destroyed houseflies and a number of other household pests. The first indications of insect resistance came in 1947 from Italy and Sweden, where it was reported that houseflies were no longer being killed by DDT. Resistance on the part of houseflies has developed in many other parts of the world during the last five years. Other insects in which this phenomenon has been reported are bedbugs, lice and fleas. In mosquitoes resistance has been encountered in *Culex pipiens* in Italy and in certain species of Aedes in the United States. No fully authenticated case of resistance in Anopheles has yet been established, but recent reports from Greece concerning *A. sacharovi* are disturbing.

But even if resistance does not become established in anopheline mosquitoes, the development of the phenomenon in other insects has unfortunate and embarrassing results in antimalarial campaigns. When houseflies, bugs, fleas and so forth have all been killed during the first year's application of an insecticide, whereas in the second year many of these insects survive the spraying, the natural reaction of the populace is to conclude that they are now being supplied with an inferior product, and the public co-operation that is essential for the success of this measure may thereby be lost. Moreover, under such circumstances it is often difficult to persuade local authorities to continue routine spraying, since the destruction of insects other than anophelines is important for the control of a number of diseases of medical importance.

Resistance is unfortunately not confined to DDT; it has also been encountered with BHC and with various diels-Adler condensation products, of which dieldrin is a member. Further researches are in progress in many countries with the object of producing a residual insecticide in which this unfortunate attribute is absent. As far as I am aware, the progress made in this direction has hitherto not been very encouraging, but the advances made in all branches of science in recent years have been so striking that I am confident that the difficulties will eventually be surmounted.

Conclusion

I have confined my remarks to aspects of research that have an obvious bearing on the control of malaria, but there are a number of other investigations now in progress that may affect the issue. One of these concerns the physiologic approach to malaria and its problems. Maegraith and his colleagues at the Liverpool School of Tropical Medicine have recently presented results of some remarkable experiments carried out with a strain of *Plasmodium berghei* in mice, in which the infection has apparently been cured by feeding the animals on a diet consisting exclusively of milk. Similar results have since been obtained with *P. cynomolgi* in monkeys both by Maegraith in Liverpool and by Garnham in London. Further studies on these lines with human volunteers are now contemplated, but it is too early to predict at this stage whether this line of research will achieve results of practical importance.

I think that from what I have said this evening it will be appreciated that much must still be learned about the problems of malaria and its control, and that despite the great advances that have been made in recent years there is urgent need for further research. There is ample scope for improving existing conditions and for devising new and more effective remedial measures; therein, for me at least, lies the great attraction of this branch of public-health activity.

EVALUATION OF A NEW ANTITUSSIVE AGENT*

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DEXTRO-3-methoxy-N-methylmorphinan§ hydrobromide (dextromethorphan hydrobromide) is an experimental drug that has shown cough-inhibiting properties in animals, but the degree of this effect in human beings was not known. Therefore, a study was undertaken to determine the antitussive effect of this substance clinically.

The merits of another compound of the morphinan series, racemic-3-hydroxy-N-methylmorphinan hydrobromide, as a potent analgesic agent are well known.[1-6] After the resolution of the racemate into its optically active isomers by Schnider and Grüssner,[7] pharmacologic studies by Randall and Lehmann,[8] Fromherz[9] and Benson et al.[10] showed that the analgesic action of racemorphan resides in its levorotatory component. Similarly, Isbell and Fraser,[11] working with drug addicts, demonstrated that the levorotatory isomer accounts for the addicting potentiality of the racemic form of the drug, its dextrorotatory form being devoid of addiction liability.

3-methoxy-N-methylmorphinan is related chemically to 3-hydroxy-N-methylmorphinan as codeine is related to morphine. Since codeine is a valuable antitussive, it seemed logical to study racemethorphan, levomethorphan and dextromethorphan — these substances were all used in their hydrobromide form — for their cough-inhibiting properties. Benson et al.,[10] by means of their new technic of electric stimulation of the trachea of the unanesthetized dog,[12] reported that all three substances gave antitussive responses. Cough inhibition was most marked with the dextro and racemic compounds, but dextromethorphan hydrobromide, in contrast to racemethorphan hydrobromide, was not productive of central depression. Therefore, it seemed of particular interest to investigate the antitussive action of the dextrorotatory form of the compound in man, which was supplied under the experimental number designation, Ro 1-5470/5.¶

Investigation of the addictive and analgesic properties of dextromethorphan hydrobromide did not enter into the primary purpose of this project. (We administered the drug for short periods only, to determine its antitussive merits.) However, at the time we embarked on the evaluation of dextromethorphan hydrobromide, it was known that the racemic form of the drug is capable of causing addiction. It was speculated, however, that by analogy, the dextrorotatory form would not be addictive, since dextrorphan is devoid of addiction liability. The truth of this postulate was demonstrated by Isbell and Fraser[13] while we were investigating the clinical effectiveness of the medication.

Dextromethorphan hydrobromide (4 mg.) was compared with a medication of known cough-inhibiting properties — namely, codeine sulfate (17 mg.) — and with placebo medication. All drugs were given four times a day: at 8:00 a.m., 12:00 noon, 4:00 p.m. and 8:00 p.m. We have previously described this method,[14] but it was attempted in this study to make the technic as precise as possible. Thus, the three materials were supplied in tablets of identical appearance and taste and were delivered as unknowns. Indeed, the study was a completely blind one in that each of the three materials was provided under three different code designations (a total of nine unknowns); these were 17, 19, 21, 28, 31, 32, 34, 38 and 41, but their true identity was not revealed to us until after completion of the project. The placebo tablets served as control medication to establish a standard of comparison. The observations were made by third parties who were not members of the research group. The medications were given in a random sequence, determined by chance selection. (It would have been preferable to give the medications in every conceivable sequence, but this would have required a figure of 9 factorial for the number of patients, or 362,880.)

The method of observation involved a scale of arbitrary values. For recording the data, the degree of cough was rated numerically from 0 to 4, 0 indicating no cough, 1 occasional, barely troublesome cough, 2 moderately troublesome cough, 3 markedly troublesome cough, and 4 incessant and distressing cough. Observations on cough and side effects were recorded four times a day by nurses, patients and doctors.

Approximately 1400 patients were screened to obtain 160 patients displaying cough of satisfactory

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§The bases of the compounds of the morphinan series referred to in this paper are listed below together with their adopted generic designations:

Chemical Designation	Generic Name
dextro-3-methoxy-N-methylmorphinan	dextromethorphan
levo-3-methoxy-N-methylmorphinan	levomethorphan
racemic-3-methoxy-N-methylmorphinan	racemethorphan
dextro-3-hydroxy-N-methylmorphinan	dextrorphan
levo-3-hydroxy-N-methylmorphinan	levorphan
racemic-3-hydroxy-N-methylmorphinan	racemorphan

For the sake of brevity, the chemical designations will be used only sparingly in this paper, the generic names being employed more often.

¶All medications for this investigation supplied by Hoffmann-La Roche, Incorporated, Roche Park, Nutley, New Jersey.

degree and duration.* All patients were given each medication for five days — a total test period of forty-five days. A five-day test period of each of the 9 unknowns was considered adequate. Actually, 65 patients, with a severe chronic cough, a number sufficient for statistical evaluation, completed the forty-five-day experimental period. All patients were started on the same day and rotated on schedule. Since there were gaps in the observations entered by patients and nurses, only the recordings made by the physicians were used for analysis. The total number of observations recorded by the doctors amounted to 65 (patients) x 4 (observations per day) x 45 (days), or more than 11,000 recordings.

TABLE 1. *Analysis of Variance — First Orientation.*

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUM OF SQUARES	MEAN SQUARE
Total	2924	2806.7530	
Between persons	64	1211.3950	18.9280
Between days	4	4.6696	1.1674
Between drugs	8	99.1870	12.3984
Residual	2848	1491.5014	0.5237
	P-VALUES	F-VALUES FOR P = 5 PER CENT	FOR P = 1 PER CENT
Persons/residual	36.14	1.30	1.44
Days/residual	2.23	2.37	3.32
Drugs/residual	23.67	1.94	2.52

The desire to identify the unknowns at an early phase of a study of this type is hard to repress. It was found that one of the doctors was carefully keeping a box score of his observations in an attempt to spot the various medications. Since such a practice would establish a factor of prejudice, it was stopped. No personal feelings were permitted to color any of the observations. The observers were soon totally confused about the significance of their recordings. In fact, some of them wanted to discontinue their efforts since they could not see any difference in the results obtained with the various medications. The entire method was simple, requiring only on-the-spot recording of a symptom and analysis of the accumulated data.

TABLE 2. *F-Values for Persons/Residual and Days/Residual for Each Drug.*

CODE NO.	F-VALUES FOR PERSONS/RESIDUAL	F-VALUES FOR DAYS/RESIDUAL
17	20.32	0.43
19	18.01	0.50
21	22.57	2.02
28	19.93	1.13
31	28.71	1.76
32	14.51	4.00
34	20.92	1.07
38	22.02	0.40
41	17.73	6.73

*The case material used in this study consisted of patients at the Long Island Hospital, Boston, and the Cambridge Tuberculosis Sanatorium, Cambridge.

The scale was sliding and relative for each patient so that only the change in degree of cough was important. The data were turned over after each five-day period for recording on master sheets.

When all data became available, they were subjected to an analysis of variance. Thus the results could be studied for significance to eliminate the possibility that chance produced them.

The initial objective was to identify the nine unknown drugs. By aggregating all recorded observations and by reducing them to simplest terms, we could arrange the nine materials according to their effectiveness (see Table 4).

The first and paramount question is whether the observed differences between these 9 values are due to chance, or whether a cough-suppressing activity of some of the 9 drugs must be accepted.

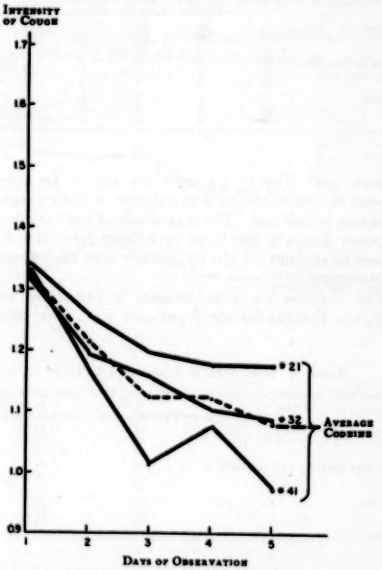

FIGURE 1. *Cumulative Effect of Codeine.*

The variations between the patients may well obscure the probable variations between the drugs if one does not use the proper statistical method.

The variation between patients is of no value as such and does not contribute significantly to the final conclusions of the study, but is of the utmost importance for the statistical analysis of the data.

Table 1 gives in the usual form the last steps of the variance analysis. We recognized four sources

of variation, of which the variance between days is of no paramount importance at this point. The variance between persons is extremely large and even larger than that between drugs. The F-values for persons/residual, as well as for drugs/residual, are far beyond the 1 per cent points — namely, 1.44 and 2.52, respectively. This means, in the first place, that the variation between the patients is extremely significant and not to be explained as a chance one. The 65 patients are not to be considered as a homogeneous population in their cough behavior in this test. The magnitude of the variance between drugs is too large as follows from the F-values to account for the hypothesis that all 9 drugs are identical.

The F-value for days/residual is just short of 2.37, the F-value for the 5 per cent level. We cannot arrive at the conclusion that the variation between days is not due to chance alone, but the F-value is large enough to demand special attention. It is not impossible that, for example, 1 drug (3 code numbers) has a *cumulative* effect, and in that case 3 out of 9 code numbers will show a probable significant difference between the five days of observation. This tendency may well be obscured in this analysis because we pool all first, second and third — and so forth — days together, disregarding the code numbers.

Summarizing this analysis of variances, we came to the following conclusions: it is extremely likely that the differences in the means or standard deviations, or both, of the 9 drug groups are due to the fact that these 9 drugs are not identical; the patients in this test do not behave as a homogeneous group; it is not impossible that one or more code numbers will show a variation between days, which cannot be explained by chance alone.

Analyses were performed to test whether the variations in the daily observations on each of the 9 drugs are due to chance, or whether one has to accept another explanation (Table 2).

From the previous test it was found that the variance between persons is extremely large, and that we must therefore compute the "between-persons sum of squares" to reduce the residual sum of squares.

It will be obvious that none of the 9 F-values for days/residual will be significant if we neglect this important source of variation. There is no doubt about the significance of the F-value for persons/residual, because it is always far beyond the 5 per cent and even the 1 per cent point (approximately 1.40 and 1.60).

It is of special interest to see which F-values for days/residual exceed the 5 per cent and 1 per cent point. The F-values for 4 and 256 degrees of freedom at the 5 per cent level are approximately 2.40 and at the 1 per cent level approximately 3.38.

The 3 lowest-ranking materials (see Table 4) showed a significant difference in activity in relation to the others in that they were the least effective; it was concluded that these 3 were placebo medication.

Because of the cumulative effect (Fig. 1) and because of a much greater incidence of side effects (Table 3) with the 3 highest-ranking materials (see Table 4) — side reactions that are typical of

TABLE 3. *Number of Patients Recorded during a Period Having Side Effects of Drugs.*

DRUG	NO. OF PATIENTS	CONSTIPATION	DROWSY AND SLEEPY	NAUSEA	TOTAL SIDE EFFECTS PER DRUG
		NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS	
Codeine	21	18	25	9	
	32	6	19	9	126
	41	10	20	10	
Dextromethorphan hydrobromide	19	2	5	2	
	31	2	1	1	19
	38	1	3	2	
Placebo	17	1	3	0	
	28	3	5	1	17
	34	2	2	0	

TABLE 4. *Rank Order of Relative Effectiveness.*

DRUG	I TEST RESULTS	II ACTUAL CODE
Codeine	41	41
	32	32
	21	21
Dextromethorphan hydrobromide	38	38
	19	19
	28	31
Placebo	31	28
	17	17
	34	34

TABLE 5. *Analysis of Variance — Codeine vs. Dextromethorphan Hydrobromide.*

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUM OF SQUARES	MEAN SQUARE
Total	1949	1645.6872	
Between patients	64	811.8485	12.6851
Between drugs	1	22.7182	22.7182
Residual	1884	811.1205	0.4305
	F-VALUES		
Patient/residual		29.46	
Drugs/residual		52.77	

TABLE 6. *Analysis of Variance — Placebo vs. Dextromethorphan Hydrobromide.*

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUM OF SQUARES	MEAN SQUARE
Total	1949	2019.7726	
Between patients	64	952.3626	14.8807
Between drugs	1	14.6986	14.6986
Residual	1884	1052.7114	0.5588
	F-VALUES		
Patient/residual		26.63	
Drugs/residual		26.31	

codeine — it was assumed that these materials were codeine.

The middle group of materials, therefore, was thought to be dextromethorphan hydrobromide.

At this point, the materials were decoded. It appeared (Table 4) that 7 of the 9 code numbers had been identified correctly, but that 1 number designating placebo was thought to be dextromethorphan hydrobromide and 1 number designating dextromethorphan hydrobromide was thought to be placebo medication.

When we learned of this transposition, the data were subjected to further analysis. It was found that the 1 batch of dextromethorphan hydrobromide (Code No. 31) that had been rated less effective than 1 batch of placebo medication (Code No. 28) followed codeine more frequently in the administrative sequence than the other medications so that the patients were disproportionately unfavorably impressed with the effect of the medication.

TABLE 7. *Analysis of Variance, Placebo vs. Codeine.*

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square
Total	1949	1803.2871	
Between patients	64	802.2544	12.5352
Between drugs	1	73.7398	73.7398
Residual	1884	927.2929	0.4922
	F-Values		
Patient/residual		25.47	
Drugs/residual		149.82	

Notwithstanding the fact that 1 placebo medication was found to be more effective than 1 dextromethorphan hydrobromide medication, the experimental drug showed a significantly greater cough-suppressing effect than the placebo.

It is now necessary to compare placebo with dextromethorphan hydrobromide, placebo with codeine and codeine with dextromethorphan hydrobromide. These analyses of variances are presented in Tables 5, 6 and 7.

From these tables it follows that both codeine and dextromethorphan hydrobromide have a definitely greater cough-suppressing activity than the placebo and that the cough-suppressing effect of codeine in a dosage of 17 mg. is superior to that of 4 mg. of dextromethorphan hydrobromide.

Figure 2 gives the day means of the 3 drug groups over the entire five-day period of observation after decodification.

If a linear relation is assumed between dose and cough-suppressing activity, 4 mg. of dextromethorphan hydrobromide has about 44 per cent of the effectiveness of 17 mg. of codeine. It is anticipated that 9 to 10 mg. of dextromethorphan hydrobromide would approximate the antitussive effect of 17 mg. of codeine. Studies in this direction are under way.

Summary and Conclusions

A blind test was carried out in 65 patients to appraise the merits of 4 mg. of dextro-3-methoxy-N-methylmorphinan hydrobromide (dextromethorphan hydrobromide) as an antitussive agent. The study included comparative trials with codeine sulfate, 17 mg. and placebo medication. Each of the 3 materials was supplied under 3 different code designations — a total of 9 unknowns, all of identical appearance and taste. These were administered for five days each, a total observation period of forty-five days. The medications were given in a random sequence. The cough-suppressing activity of the drugs was recorded by means of a numerical scale.

After aggregating more than 11,000 observations and reducing them to simplest terms, we made an attempt to identify the materials. Seven of the 9 unknowns were thus identified correctly. Mathematical treatment of all data revealed that the 3 groups of drugs showed statistically significant cough-suppressing properties. The antitussive effectiveness of 4 mg. of dextromethorphan hydrobromide was approximately half that of 17 mg. of codeine. The incidences of side effects of dextromethorphan hydrobromide at the dosage level used and of placebo tablets were of the same order of

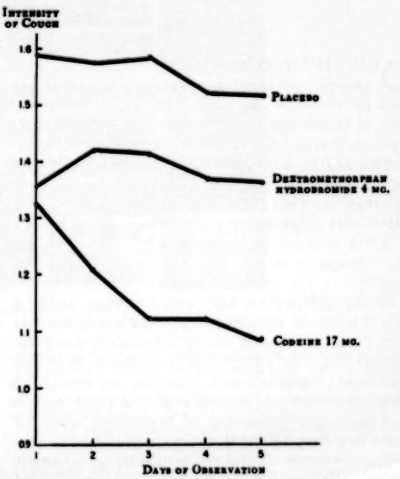

FIGURE 2. *Day Means of Cough-Suppressing Effectiveness of Three Drugs over the Entire Period of Observation.*

magnitude. However, the incidence of reactions to codeine was distinctly higher.

It is concluded that dextromethorphan hydrobromide is an effective antitussive agent and is free of side effects.

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ACUTE PERICARDITIS ASSOCIATED WITH INFECTIOUS MONONUCLEOSIS*

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DESCRIPTIONS of the syndrome of acute nonspecific or idiopathic pericarditis appearing since the report by Barnes and Burchell[1] have added little to knowledge of the subject. They have, however, emphasized the variability of this type of pericarditis and have suggested to some the concept that the etiology may likewise be diverse. It is interesting that in 1947 Burchell,[2] commenting on the differential diagnosis, stated: "When the diagnosis of acute pericarditis seems evident, the search for an etiologic factor should not be abandoned too quickly."

Benign pericarditis has been reported under a wide variety of circumstances. The syndrome has been noted to follow many respiratory-tract infections such as pharyngitis, nasopharyngitis and tonsillitis,[3] sinusitis[4] and atypical pneumonia.[5, 6] Bing[7] described an epidemic of acute pericarditis in Copenhagen consisting of 6 patients admitted to a single hospital ward within several weeks, each with a diagnosis of Bornholm disease or epidemic myositis. Benign pericarditis has also been reported as a postoperative complication of various surgical procedures,[8,9] as occurring during major attacks of bronchial asthma[10] and as part of an allergic reaction associated with serum sickness after injection with tetanus antitoxin and other foreign proteins.[11, 12] A benign case of pericarditis and eosinophilic pleurisy with effusion has also occurred spontaneously in a hypersensitive person.[13]

The purpose of this report is to present 3 cases and to emphasize the relation of acute pericarditis to infectious mononucleosis.

Case Reports

CASE 1. J. S., a 26-year-old man was admitted to the Thomas England General Hospital on February 7, 1945, complaining of malaise, fever and sore throat. The patient had previously been admitted to the hospital on January 25 with fever, chills and generalized malaise. Physical examination revealed moderate hyperemia of the pharynx, with an enlarged, tender left anterior cervical lymph node. The remainder of the examination was normal. The white-cell count was 9500, with 50 per cent neutrophils, 40 per cent lymphocytes, 2 per cent eosinophils and 8 per cent monocytes. The patient improved on symptomatic therapy and was discharged on January 31. He felt poorly until February 6, when a severe sore throat, persistent fever and tender enlarged cervical lymph nodes developed. On February 7 he had a chill, nonproductive cough and lower substernal pain.

Physical examination showed an acutely ill, slightly dyspneic man. The pharynx was moderately hyperemic; the tonsils had been removed. A small tonsillar tag with a follicle of whitish exudate was seen in the left tonsillar fossa. The lungs were clear; the heart was not enlarged to percussion. The rhythm was regular, and no murmurs were audible. The tip of the spleen was palpable below the left costal margin on deep inspiration; it was soft and nontender. The anterior and posterior chain of cervical lymph nodes and the axillary and inguinal lymph nodes were significantly increased in size.

The temperature was 102.4°F., the pulse 92, and the respirations 24. The blood pressure was 106/60.

Examination of the blood disclosed a red-cell count of 5,100,000, with a hemoglobin of 16.5 gm. per 100 cc., and a white-cell count of 13,100, with 84 per cent lymphocytes. Many of these lymphocytes were atypical and suggestive of infectious mononucleosis. The urine was clear. Heterophil-antibody agglutination was later reported positive in a dilution of 1:1792. The sedimentation rate (Westergren method) was 38 mm. per hour. Two blood cultures were sterile, and the usual agglutination tests and smears for malaria parasites were negative.

On the 2d hospital day, the patient complained of increasingly severe knife-like pain in the substernal region radiating to both scapular regions and to the left shoulder. The pain was aggravated by coughing, deep inspiration and lateral movements of the trunk. Examination of the heart disclosed distant

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heart sounds and a loud pericardial friction rub. An x-ray film of the chest showed the cardiac silhouette to be moderately enlarged. An electrocardiogram (Fig. 1) demonstrated T-wave changes consistent with the diagnosis of acute pericarditis.

On symptomatic therapy, the temperature gradually subsided, returning to normal on the 7th day; the pericardial friction rub disappeared on the 4th day, and the pain was entirely relieved by the 8th day. Repeated x-ray films of the chest disclosed a gradual decrease in the size of the heart shadow, and serial electrocardiograms (Fig. 1) showed a gradual return of the negative T waves to positivity. Numerous blood counts were performed. On February 18, the heterophil-antibody titer was positive in dilutions as high as 1:3584 and the white-cell count was 6800, with 79 per cent lymphocytes. At the time of discharge on March 3, the titer was still positive in a dilution of 1:224.

Case 2. W. R., a 25-year-old man, was admitted to the Veterans Administration Hospital, Davis Park, Providence, on August 10, 1950, complaining of pain in the anterior part of the chest. The patient had been well until the morning of admission, when, on arising, he noted a severe pain across his entire chest. It was persistent, did not radiate and was not associated with dyspnea. The pain persisted all morning and later in the day it was localized to the substernal region and was felt mostly on deep inspiration. There had been no previous upper respiratory infection.

Physical examination revealed a well developed, well nourished man who was not acutely ill. The pharynx was reddened. The lungs were clear. The heart was not enlarged to percussion; the rhythm was regular, and no murmurs were heard. The striking finding on auscultation was a loud to-and-fro pericardial friction rub. The remainder of the examination was not remarkable.

The temperature was 101°F., the pulse 100, and the blood pressure 120/70.

Examination of the blood disclosed a normal hemoglobin and red-cell count; the white-cell count was 6900, with 85 per cent neutrophils, 10 per cent lymphocytes and 5 per cent monocytes. The urine gave a + test for albumin and a negative test for sugar; there were a few red blood cells and occasional large granular casts in the sediment. A blood culture was sterile, and the blood Kahn reaction was negative. An x-ray film of the chest showed the heart to be normal in size and shape, with no definite evidence of pulmonary disease.

The patient ran an elevated temperature to 102°F. for the first 3 days. He then became afebrile for the next 4 days. During the first 4 days he was on aureomycin therapy. When the drug was discontinued the temperature began to rise, reaching 102°F. on the 11th day. Another examination of the blood revealed a white-cell count of 14,100, with 71 per cent lymphocytes, of which 61 per cent were atypical. Heterophil-antibody agglutination was positive in a dilution of 1:224. In addition, a severe sore throat, with enlargement of cervical and axillary lymph nodes, developed. He was again placed on aureomycin, the sore throat disappeared, and the temperature returned to normal. The pericardial friction rub disappeared after the first day in the hospital. Serial electrocardiograms (Fig. 2) were consistent with the diagnosis of pericarditis. The patient was discharged against advice on September 6, 1950.

Case 3. G. J., a 19-year-old Negress, was admitted to the Rhode Island Hospital on August 6, 1952, complaining of headache and chest pain. The patient had been well until 10 days previously, when a frontal headache and pain in the anterior part of the chest developed. The pain was most marked over the midsternum. It was persistent and was made worse by cough or deep inspiration. The pain and headache gradually subsided so that at the time of admission the chest pain was mild and only present on deep inspiration and on bending forward. The patient experienced several bouts of nausea and vomiting during her illness but had no epistaxis, joint pains or profuse sweating.

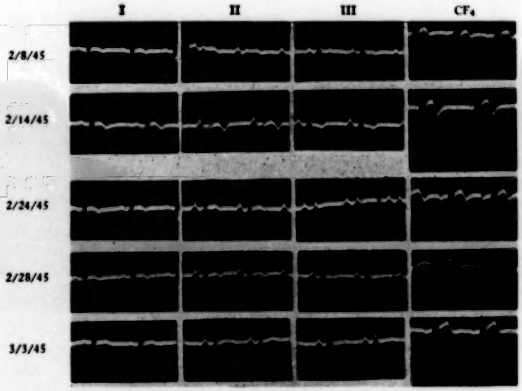

Figure 1. *Electrocardiograms in Case 1.*

Physical examination revealed a well developed, well nourished woman who was not acutely ill. The tonsils were hypertrophied. The anterior cervical and left posterior cervical lymph nodes were enlarged. The lungs were clear. The heart was not enlarged to percussion; the rhythm was regular, and no murmurs were heard. A pericardial friction rub was audible over the entire precordium, loudest over the 3d and 4th left interspaces. The remainder of the examination demonstrated no significant abnormalities.

The temperature was 101°F., the pulse 118, and the respirations 18. The blood pressure was 105/60.

Examination of the blood showed a red-cell count of 3,740,000, with a hemoglobin of 11.2 gm. per 100 cc., and a white-cell count of 4900, with 75 per cent neutrophils, 23 per cent lymphocytes and 2 per cent monocytes. The sedimentation rate (Westergren method) was 30 mm. per hour; the hematocrit was 35 per cent. The urine was clear. Two blood cultures were sterile, and the blood Hinton reaction was negative.

Aureomycin administration was begun, and the temperature slowly fell, reaching normal by the 9th hospital day. The chest pain and pericardial friction rub disappeared after 4 days. An x-ray film of the chest on August 7 showed the heart to be enlarged, with a transverse diameter of 15.7 cm. as compared with an intrathoracic diameter of 24 cm. On August 11 another film revealed a reduction of the transverse diameter of the

heart to 14 cm. Serial electrocardiograms (Fig. 3) were consistent with the diagnosis of acute pericarditis. Aureomycin was discontinued on August 18, and on August 20 a severe sore throat, reddened pharynx, exudate on the right tonsil and enlarged anterior, posterior cervical and left axillary lymph nodes developed. The white-cell count on August 23 was 5700, with 58 per cent lymphocytes, many of which were atypical and suggestive of infectious mononucleosis. The heterophil-antibody titer was reported positive in dilutions of 1:160 on August 26 and in dilutions of 1:320 on September 2. The temperature rose to 104°F. and fell to normal on intravenous administration of aureomycin. The patient was discharged on September 3.

Discussion

These 3 patients varied in age from nineteen to twenty-six years. Each illness was associated with an upper respiratory infection characterized by fever, sore throat, cervical lymphadenopathy and variable degree of malaise. In 1 case the respiratory infection preceded and in the others it followed the pericarditis. In each case clinical, hematologic and serologic evidence of infectious mononucleosis appeared at some time during the course of the illness. A pericardial friction rub was audible in each case; it persisted from one to four days. Typical electrocardiographic changes of acute pericarditis appeared simultaneously. In 2 cases the electrocardiograms showed transient elevation of the RS-T segments consistent with the acute stage; in all, the subacute pattern characterized by T-wave inversion in some or all of the standard and precordial leads was present. Serial roentgenograms of the heart revealed enlargement of the cardiac silhouette in 2 cases; this disappeared during the hospital course.

Interesting case reports and brief but informative reviews of the subject of cardiac involvement in infectious mononucleosis are readily available in the medical literature.[14-17] The reviews indicate that the cardiac complications are usually subclinical and benign and manifested by transient, nonspecific electrocardiographic alterations. These consist of T-wave abnormalities, disturbances in auriculoventricular conduction, slight depression of the RS-T segments and minor arrhythmias. There is apparently no correlation between the electrocardiographic deviations and clinical findings and the severity of the disease.

In recent years autopsy confirmation of the existence of myocarditis in infectious mononucleosis has become available. Custer and Smith[18] found the basic lesion to be a perivascular infiltration of

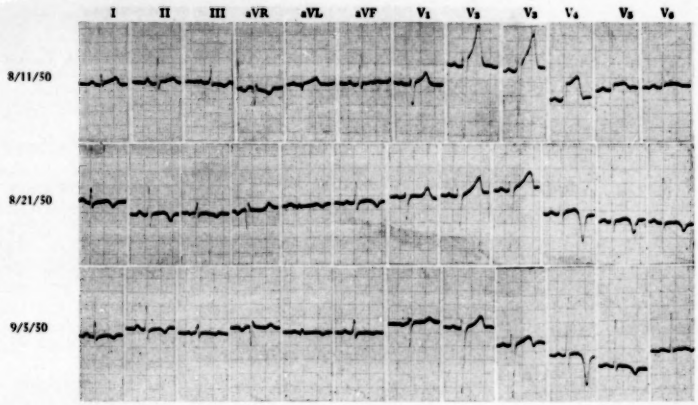

Figure 2. *Electrocardiograms in Case 2.*

both normal and abnormal lymphocytes. They believed these cells to be metaplastic and to be formed in situ from other cells of the reticuloendothelial system. The myocardial and pericardial lesions were minimal and unassociated with any necrosis of the muscle or with serosal reaction. Despite the fact that there are as many lesions in infectious mononucleosis as there are organs and tissues of the body, it is surprising that the pericardium is so rarely involved.

Evans and Graybiel[19] reported 4 cases of infectious mononucleosis with electrocardiographic changes consisting primarily of depression or inversion of the T waves. These abnormalities persisted for six to forty-one days. The authors considered the T-wave changes to be the result of pericardial involvement because they "persisted over a longer period of time than would be expected if the myocardium alone was affected." In 1 of their cases a pericardial friction rub developed on the

fifth day of illness. In a fifth case a twenty-year-old boy had substernal pain radiating across the left side of the chest. The heart was moderately enlarged, the sounds were of poor quality, and a pericardial friction rub was audible in the third and fourth intercostal spaces to the left of the sternum. A diagnosis of pericarditis with effusion was made, and the patient admitted to the hospital. Complete studies, including examination and culture of the pericardial fluid on several occasions, failed to establish an etiologic diagnosis. The only definite finding was a positive heterophil-antibody test in dilutions as high as 1:896. It was believed that rheumatic pericarditis after infectious mononucleosis. Bradshaw,[20] in a discussion of the possible relation of infectious mononucleosis to rheumatic fever, reported the case of a seventeen-year-old girl who was known to have had a normal heart previously and who, 6 weeks after recovery from an attack of infectious mononucleosis, was found to have evidence of mitral stenosis. The sequence of events favors the view that the murmur had been present and inaudible before the attack of infectious mononucleosis. The absence of any signs and symptoms of rheumatic fever, the previous history, the benign course and the lack of any

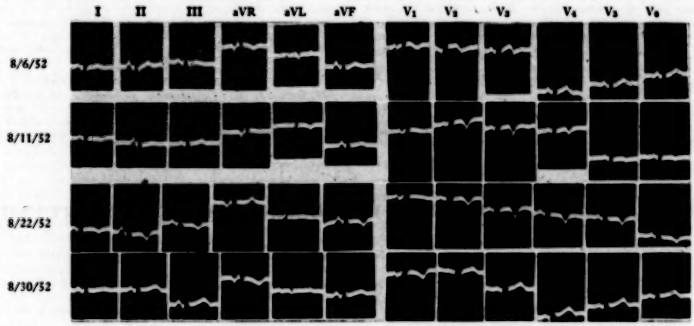

FIGURE 3. *Electrocardiograms in Case 3.*

the pericarditis was probably a complication of infectious mononucleosis.

De Fazio and Marsico[14] reported a single case of infectious mononucleosis in a forty-two-year-old man who manifested pain in the left scapular region that was aggravated by breathing and coughing and gradually moved around to the precordial region. Examination revealed a pericardial friction rub, x-ray evidence of cardiac enlargement and serial electrocardiographic changes consistent with acute pericarditis.

The interpretation and significance of the cardiac findings in these cases of infectious mononucleosis require critical evaluation. In view of the development of the symptoms, clinical signs and electrocardiographic changes during the acute illness, it seems unlikely that they were merely coincidental. The small number of patients affected, however, brings up the remote possibility of the coexistence of two independent diseases—namely, acute idiopathic pericarditis and infectious mononucleosis. In the absence of any specific test for idiopathic pericarditis, such a diagnosis is not possible.

Another possibility that might be considered is whether cases such as those reported above represent cardiac residua indicate that these were not cases of rheumatic fever.

In a consideration of the pathogenesis of acute pericarditis in infectious mononucleosis, several possibilities are to be considered. The first is the proximity of the hilar lymph nodes with extension of the infection into the pericardial sac. Another is a virus infection of the pericardium. Although the etiologic agent has not been identified, it is generally accepted that infectious mononucleosis is a generalized disease of viral origin. That viral agents may cause a benign form of pericarditis has been demonstrated in a case of lymphogranuloma venereum.[21] The final possibility is a response of the pericardium as a shock organ to an offending allergen in a sensitive person. This theory readily explains many forms of pericarditis,[10, 12, 13, 22] offers the interesting hypothesis that many etiologic factors may cause the clinical picture of acute idiopathic pericarditis and suggests that one is dealing not with a specific disease but rather with a clinical syndrome resulting from a variety of causative agents.[22]

Summary

Three cases are reported in which clinical and electrocardiographic evidence of acute pericarditis occurred during the acute phase of infectious mononucleosis. The literature on the subject is reviewed.

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USE OF A NEW ORAL DIURETIC, DIAMOX, IN CONGESTIVE HEART FAILURE

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CLASSIC treatment for water retention in congestive heart disease has involved the use of mercurial and other substances that affect the renal tubules in such a way as to decrease the reabsorption of electrolytes and water. Recently, a new principle has been introduced for the treatment of water and salt retention in the form of Diamox,† a specific inhibitor of carbonic anhydrase.[1-4] The results of such inhibition are to promote the renal loss of bicarbonate, sodium, potassium and water.

Preliminary clinical data indicated that this effect could be obtained in patients with congestive heart failure.[5] The object of the present study was to find whether such patients could be kept free of edema and with relief of symptoms over a prolonged period. In this connection it was of interest to find to what extent the drug could replace mercurial injections in ambulatory patients.

Case Reports

Case 1. H. W., a 74-year-old married woman with arteriosclerotic heart disease and hypertension of 15 years' duration, complained of dyspnea, nocturnal distress, orthopnea and edema of the lower extremities over a period of 6 years. The heart was enlarged, and there was a Grade 2 systolic murmur over the apex, transmitted to the axilla. The blood-pressure was 210/80. There were moist rales in both bases. The liver edge was enlarged to the crest of the ilium. There was ++ to +++ pitting edema of the lower extremities. The urine had a specific gravity of 1.018 and gave negative tests for albumin and sugar.

The sediment contained 4 to 10 white cells per high-power field. A blood count was normal. An electrocardiogram demonstrated notched and slurred QRS complexes in Leads 1 and 2, depressed ST segments in Leads 1 and 2, AVF, V_5 and V_6 and inversion of the T waves in Leads 1, aVF, V_5, V_6 and V_6.

The patient had been on a cardiac regimen with maintenance dose of Digoxin, 0.5 mg. daily, a diet containing 2 gm. of salt and injections of Mercuhydrin (2 cc.) at weekly intervals. On this therapy she was free of edema for about 5 days, after which fluid recurred, with frequent episodes of acute pulmonary edema.

Diamox was substituted for Mercuhydrin on June 4, 1952, 0.5 gm. twice a day. About 3 hours after the first dose the patient voided 600 cc. of urine. She lost 4 pounds in weight after the 1st day of treatment. Owing to unpleasant side effects of the drug, such as paresthesia of the face and hands and sleepiness, the dose was reduced to 0.5 gm. once a day on the following day. This dose was further reduced to 0.25 gm. daily. After 2 months, and on this schedule, together with Digoxin, she has been kept edema free, with her weight more or less constant (within 1 or 2 pounds) for the past 6 months. She has not required any mercurial injections during this time. She has had no attacks of nocturnal dyspnea and no edema of the lower extremities.

There were no appreciable side effects from this dosage of the drug.

Case 2. A. R., a 61-year-old man with chronic rheumatic heart disease and mitral stenosis, had several episodes of congestive heart failure with pulmonary edema over a period of 6 months. He gave a history of rheumatic fever in 1936, when he was in bed for 5 months. When first seen in February, 1952, he was orthopneic and dyspneic on mild exertion. The heart was enlarged, and there was a palpable presystolic apical thrill,

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†Diamox (previously known as 6063, its serial designation in the Chemotherapy Division, Stamford Research Laboratories of the American Cyanamid Company) is the trademark of Lederle Laboratories Division of the American Cyanamid Company for acetazolesamide or 2-acetylamino-1, 3, 4-thiadiazole-5-sulfonamide.

with a presystolic murmur over the apex. The liver edge was just palpable and tender. There were a few moist rales in the bases. There was a Grade 1 to 2 pitting edema of both legs. The blood pressure was 160/90, and the pulse was regular. The urine had a specific gravity of 1.010, with 1 or 2 white cells per high-power field in the sediment. A blood count was normal. An electrocardiogram showed left-axis deviation, sinus rhythm, with tall, peaked P waves in Leads 2 and 3 and small T-waves in Leads V_4 and V_5.

The patient had been maintained on Digoxin, 0.25 mg. twice a day, a low-salt diet and Mercuhydrin, 2 cc. parenterally at 2-week intervals. On this regimen his progress was unsatisfactory, since he required Mercuhydrin injections every 7 to 14 days, and the toxic effects of the injections were particularly distressing. The edema of the legs and dyspnea began to reaccumulate 6 to 10 days after each injection.

Diamox, 0.5 gm. twice a day, was substituted for Mercuhydrin on July 4. After several days, this dose was reduced to 0.5 gm. daily because of drowsiness and paresthesia of the face. These signs disappeared on the lower dose. The patient has given no evidence of myocardial decompensation since then, and for the past 5 months has been edema free, his weight varying between 152 and 154 pounds. No Mercuhydrin has been required during this time.

Case 3. A. P., a 42-year-old man with arteriosclerotic heart disease and bronchial asthma, had massive anasarca, with edema fluid oozing from his legs, when he was first seen in December, 1951. He had been treated for severe congestive heart failure since July, with parenteral injections of Mercuhydrin, 2 cc. twice a week, a diet containing 1 gm. of salt and Digoxin, 0.25 gm. twice a day. On this program, a low sodium and chloride syndrome developed. After stabilization of his electrolyte status, the therapy was continued as above, except for 1 injection of Mercuhydrin weekly. This regimen was unsatisfactory because of frequent episodes of pulmonary edema during intervals between mercurial injections.

On June 4, Diamox, twice a day, was substituted for Mercuhydrin. In the ensuing 7 days the patient lost 10 pounds in weight. Because of drowsiness and paresthesia, the dose was then reduced to 0.5 gm. daily. On this schedule he has remained edema free for the past 6 months. There have been no objective signs of drowsiness or other toxic manifestations. He is actively engaged in business, and manifests no dyspnea or precordial distress in his usual duties.

Case 4. A 72-year-old unmarried woman with arteriosclerotic heart disease complained of nocturnal dyspnea, extreme exertional dyspnea and on several occasions severe pulmonary edema requiring hospitalization.

The heart was enlarged, and there was a Grade 2 systolic murmur at the apex. The rate was 120 and regular. The blood pressure was 160/96. The liver edge was felt 4 fingerbreadths below the right costal margin and was tender. There was a Grade 3 pitting edema of both lower extremities. The urine had a specific gravity of 1.016 and gave a + test for albumin and a negative test for sugar. The blood count was normal. An electrocardiogram showed an intraventricular conduction disturbance with left bundle-branch block.

The patient had been maintained on the usual cardiac regimen of low-salt diet, 0.25 mg. of Digoxin twice a day and weekly injections of Mercuhydrin, 2 cc. On this program, the symptoms noted above recurred during intervals between injections. On June 6, 1952, Diamox, 0.5 gm. twice a day, was substituted for the mercurial injection. On this dose she complained of extreme lassitude, drowsiness and paresthesia of the face and hands. However, after the daily dose had been decreased to 0.5 gm., these unpleasant symptoms were reduced to a minimum. The patient has been maintained for the past 6 months with no evidence of dependent edema. The liver has fluctuated in size, the edge being palpable from 2 fingerbreadths below the right costal margin to normal limits. The weight has fluctuated between 114 and 116 pounds. The exertional dyspnea has been considerably reduced, and there is no dyspnea at rest.

Case 5. M. S., a 60-year-old married woman, with arteriosclerotic heart disease and bronchial asthma, complained of precordial pain, orthopnea and dyspnea on effort, and edema of the lower extremities for 5 years. The heart sounds were muffled and distant; no murmurs were heard. The lungs were emphysematous, and there were numerous moist and sibilant rales throughout. The tender liver edge was felt 3 fingerbreadths below the right costal margin. The blood pressure was 140/80. The pulse was regular. There was a Grade 2 pitting edema of both lower extremities. Examination of the urine was negative. The blood count was normal. An electrocardiogram showed low voltage in the limb leads: the T wave was isoelectric in Lead 1, with ST-segment depression in Leads 2, V_4 and V_5.

The patient had been maintained on Digoxin, a low-salt diet and injections of Mercuhydrin, 2 cc., at weekly intervals. On this schedule the complaints noted above were manifest, particularly at intervals between injections. On June 7, 1952, Diamox, 0.5 gm. twice a day, was substituted for Mercuhydrin. There was prompt diuresis, and a corresponding improvement in general welfare. There was a gradual loss of weight (from 218 pounds on June to 189 pounds on December 1). Because of drowsiness and paresthesia, the original dosage schedule of Diamox was altered to 0.5 gm. a day, with elimination of unpleasant side effects. The symptoms have been considerably improved. The exertional dyspnea and orthopnea have been very much reduced. The patient has no edema of the lower extremities, and the liver edge is no longer palpable. With the exception of occasional attacks of mild bronchial asthma, the cardiac status is satisfactory.

Case 6. Mrs. M. S., a 68-year-old married woman with arteriosclerotic heart disease, complained of edema of the lower extremities and moderate dyspnea on effort of 3 months' duration. The heart was enlarged, with a Grade 1 systolic murmur over the apex. The blood pressure was 160/90. The pulse was regular. The lungs were clear. The liver and spleen were not palpable. There was Grade 2 pitting edema of both lower extremities. Examination of the urine was negative. The blood count was normal. An electrocardiogram showed sinus rhythm and left-axis deviation, with inverted T waves in Leads V_4 and V_5.

The patient was placed on a low-salt diet for 1 week, without Diamox or other therapy. There was no change in the symptoms, weight or edema of the lower extremities. She was then given Diamox, 1.0 gm. daily, on June 4, 1952. There was prompt diuresis. After 1 week on this therapy alone she lost 6 pounds in weight. She stated that she could "walk easier" and was able to "sleep better," and leg edema was absent at this time. However, because of drowsiness and paresthesia of the face and fingers, the dose of Diamox was reduced to 0.5 gm. a day, and on this dosage there were no side effects and the cardiac status was satisfactory.

The patient discontinued Diamox 3 months later, and soon dyspnea on effort and edema of the lower extremities developed, with a gain of 4 pounds in weight. Upon resumption of Diamox, 0.5 gm. once a day, she lost 5 pounds within a week and was edema free.

Case 7. J. L., a 69-year-old man with arteriosclerotic heart disease, complained chiefly of severe substernal pain on effort and ankle edema, for 6 years. He had several episodes of congestive heart failure in 1951.

He was orthopneic and there was moderate cyanosis of the lips and nails. The heart was enlarged, and there was a Grade 2 systolic murmur at the apex and over the base of the heart. The blood pressure was 150/90, and the pulse was regular. There were crepitant rales in both bases of the lungs. The liver was not palpable. There was Grade 2 pitting edema of both lower extremities. The urine and the blood count were normal. An electrocardiogram showed sinus rhythm with depressed ST segments in Leads 1, 2 and V_5.

The patient had been maintained on a low-salt diet (2.0 gm.), Digoxin, 0.25 mg. twice a day, and injections of Mercuhydrin, 2 cc., at weekly intervals. On this regimen the pretibial pitting edema persisted more or less from week to week. On July 3, 1952, Diamox, 0.5 gm. a day, was begun. By July 19 he was edema free and noted a decrease in frequency of attacks of angina pectoris. Since the institution of Diamox therapy, he has exhibited mild pitting edema of the lower extremities only occasionally and briefly. His weight has fluctuated within 2 or 3 pounds, and he has not required any mercurial injections.

Case 8. A. Z., a 54-year-old married woman with arteriosclerotic heart disease and hypertension, complained of dyspnea on mild exertion, cough and swelling of the lower extremities for 5 years. Examination showed cyanosis of the lips and nails. The heart was enlarged, and a Grade 3 blowing systolic murmur was heard over the entire precordium. The aortic second sound was tambour-like in quality. The blood pressure was 240/140. The pulse was regular. The lungs were clear. The liver edge was just palpable and tender. There was Grade 3 pitting edema of both lower extremities. Examination of the urine was nega-

tive. The blood count was normal. An electrocardiogram showed sinus rhythm and a pattern consistent with left-sided heart strain.

The patient had been on a cardiac regimen of a low-salt diet, Digoxin, 0.25 mg. twice a day, and Mercuhydrin, 2 cc. at intervals of 1 or 2 weeks for the past 3 years. The Mercuhydrin was replaced by Diamox, 0.5 gm. twice a day, on June 10, 1952, when she weighed 173 pounds. She lost 4 pounds during the 1st 2 days of therapy. The dose was reduced to 0.5 gm. daily on June 21, because of drowsiness and paresthesia of the extremities and face. Three months later the patient still complained of some drowsiness. As a result, the dose was reduced to 0.25 gm. a day. On this schedule, there was no recurrence of edema. Dyspnea on exertion was only moderate, and the patient was able to do a reasonable amount of housework. She has been maintained on this dosage schedule to the present and has no required any injections of mercurial diuretics. There have been no side effects from the drug on this dosage.

Case 9. I. P., a 40-year-old married woman, had chronic rheumatic heart disease, mitral stenosis, auricular fibrillation and hypertension. She was in extreme respiratory distress. She was orthopneic and dyspneic, and there was moderate cyanosis of the lips and nails. The neck veins were distended in the upright position, and in the horizontal they were extremely distended, the facial veins also being involved. The heart was markedly enlarged, and there was a rumbling presystolic apical murmur with accentuation of the 1st sound over the mitral area. A palpable thrill was felt over the apex. The blood pressure was 260/130, and auricular fibrillation was present. There were dullness and diminished breath sounds in the right base, with moist rales in both pulmonary bases. The liver edge was firm and nontender and extended to the iliac crest. The spleen was not palpable. There was Grade 3 pitting edema of both lower extremities and edema over the sacrum. The urine gave a ++ test for albumin and had a fixed specific gravity of 1.004. An electrocardiogram showed auricular fibrillation, with frequent ectopic ventricular beats.

The patient had been maintained on a regimen of a diet containing 1 gm. of salt, with Digoxin, 0.25 mg. twice a day; and Mercuhydrin, 2 cc., had to be administered every 4 days in an attempt to prevent rapid increase in edema fluid.

On July 14, 1952, administration of Diamox, 1.0 gm. twice a day, was begun. The edema and ascites increased, nevertheless, but at a slower rate, the patient requiring Mercuhydrin every 10 days. For 2 months on this therapy her condition deteriorated, and extreme anasarca developed. She became unresponsive to both Diamox and Mercuhydrin. The daily urine output was more or less fixed at 500 or 600 cc. The blood nonprotein nitrogen was 68 mg. per 100 cc. Cephalin flocculation was ++ in 24 and ++++ in 48 hours. The blood showed a red-cell count of 3,800,000, with a hemoglobin of 10 gm., and a white-cell count of 10,100.

An abdominal paracentesis was done, with removal of 4500 cc. of clear, amber fluid. There was a prompt improvement in diuresis after this procedure, and the patient has been maintained on Diamox, 0.5 gm. a day, with a weekly injection of Mercuhydrin. On this regimen the daily urine output has been 800 to 1200 cc. with a fixed specific gravity of 1.004 to 1.006, representing improvement in diuresis. Although her present condition is far from satisfactory and she is extremely orthopneic and dyspneic, the accumulation of edema fluid is less rapid and supplementary injections of Mercuhydrin are fewer. She states that she is much more comfortable than she had previously been, is less dyspneic and sleeps much better.

Case 10. M. M., a 70-year-old married woman with arteriosclerotic heart disease and diabetes mellitus, had been treated for congestive heart failure for the past 5 years; her condition gradually deteriorated so that she had been completely bed ridden for the past year. She had had extreme dyspnea and orthopnea, with chronic cough and edema of the lower extremities.

The heart sounds were distant, and there was a Grade 2 apical, blowing systolic murmur. The blood pressure was 180/100, and there was auricular fibrillation. The lungs were moist in both bases. The liver was not tender, and the edge was felt 4 fingerbreadths below the right costal margin. There was Grade 4 pitting edema of both lower extremities. The urine gave a ++ test for albumin and a negative test for sugar; the sediment contained an occasional hyaline and granular cast. Examination of the blood revealed a red-cell count of 4,100,000, with a hemoglobin of 10 gm., and a white-cell count of 9000. The nonprotein nitrogen was 47 mg., and the fasting blood sugar 160 mg. per 100 cc. An electrocardiogram showed auricular fibrillation with the pattern of strain of the left ventricle.

The patient had been maintained on a low-salt diet, 0.25 mg. of Digoxin three times a day, and 2 cc. of Mercuhydrin on an average of every 4 to 7 days. Her response to Mercuhydrin was erratic. Diamox therapy, 1 gm. daily, was begun on July 25, 1952. There was no diuresis or weight loss in the ensuing 6 days. On the 7th day she was given 2 cc. of Mercuhydrin, with urinary loss of 2 liters. Because of paresthesias and drowsiness, the dose of Diamox was reduced to 0.5 gm. daily, with supplementary injections of Mercuhydrin given at 2-week intervals. Gradually, the daily urine output was reduced to 400 or 500 cc., and despite increased frequency of the mercurial injections (every 5 to 7 days), together with 0.5 gm. of Diamox a day, anasarca developed. The urine gave a ++++ test for albumin, with a fixed specific gravity between 1.002 and 1.006. The nonprotein nitrogen was 55 mg. per 100 cc., and the serum chloride 102 milliequiv. per liter. The cephalin flocculation was + in 24 and +++ in 48 hours.

An abdominal paracentesis resulted in withdrawal of 5 liters of clear, amber-colored fluid, after which the patient felt relieved in general. The average daily urine output increased to 800 cc., with a + to ++ test for albumin. The specific gravity was still fixed at low levels. Diamox, 0.5 gm. daily, was continued, with much better control of edema since supplementary injection of Mercuhydrin was not necessary until 3 weeks later, when the patient had regained 3 pounds of weight, representing a much slower rate of accumulation of edema fluid. Her general condition, however, is far from satisfactory, since she is very dyspneic at rest and is completely bed ridden. She has not complained of drowsiness or other symptoms that could be attributed to the drug.

Case 11. L. D., a 72-year-old man, had had arteriosclerotic heart disease for 6 years. He had had an attack of coronary occlusion 6 years previously. He was dyspneic on mild exertion and had a productive cough. The significant physical findings included a moderately enlarged heart, with a Grade 2 blowing, apical murmur, heard also over the base of the heart. There was moisture in both lung bases, and there was a moderate pleural effusion in the right base. The blood pressure was 210/90, and the pulse was regular. The liver edge was palpated 3½ fingerbreadths below the right costal margin. There was no edema of the lower extremities. An electrocardiogram showed sinus rhythm, with the pattern of right bundle-branch block. The blood count was normal. The urine contained a faint trace of albumin.

The patient was placed on a low-salt diet (1 gm.) with 0.25 mg. of Digoxin twice a day, on which regimen he continued for 2 months without change in weight or in the size of the liver.

Diamox, 0.5 gm. daily, in addition to the therapy described above, was then begun. He lost 6 pounds of weight in 1 week and was less dyspneic and felt "stronger." The lungs were clear, and the pleural effusion that had been present for the previous 2 months had now completely subsided. The liver edge was felt 2 fingerbreadths below the right costal margin.

Case 12. H. V., a 47-year-old married woman, had chronic rheumatic heart disease, mitral stenosis, aortic insufficiency, auricular fibrillation and hypertension. She had had rheumatic fever in childhood. She complained of dyspnea on slight exertion, orthopnea and frequent episodes of palpitation.

Physical examination showed an orthopneic and dyspneic woman. The heart was enlarged, and there was a palpable presystolic apical thrill; a characteristic presystolic mitral murmur and a blowing, diastolic murmur were heard in the third left interspace. The blood pressure was 180/96. There was a Grade 2 pitting edema of the lower extremities. The liver and spleen were not enlarged. An electrocardiogram demonstrated right-axis deviation, auricular fibrillation and digitalis effect. The blood count was normal. Examination of the urine was negative.

The patient was maintained on a cardiac regimen of a diet containing 1 gm. of salt and 0.25 mg. of Digoxin twice a day, with an occasional injection of Mercuhydrin at intervals of 2 or 3 weeks for the next 2 years. On October 9, 1952, a trial with Diamox, 0.5 gm. daily, was begun. Mercuhydrin was discontinued. At this time her weight was 173 pounds; the liver edge was felt 4 fingerbreadths below the costal margin, and the rest of the physical findings were unchanged. Four days later

she returned, feeling less dyspneic. She had lost 5 pounds in weight, and the liver edge was just palpable and not tender. Since then her weight has been maintained at about 167 pounds. She had had no edema of the lower extremities, and the liver edge has been barely palpable below the right costal margin.

Case 13. W. S., a 63-year-old man, with probable rheumatic heart disease and mitral insufficiency, complained of weakness, increasing exertional dyspnea and ankle edema for a period of 3 years. Physical examination revealed mild cyanosis of the lips and an enlarged heart, with a Grade 2 blowing systolic murmur over the apex, transmitted toward the axilla. There were coarse, moist rales in both bases. The blood pressure was 150/90. The pulse was regular. The liver edge was felt 2 finger-breadths below the right costal margin. There was Grade 4 pitting pretibial edema.

Fluoroscopic examination showed extreme enlargement of the left ventricle in both the inflow and outflow tracts. There was horizontal and vertical enlargement of the left atrium, which elevated and constricted the left main bronchus. There was marked pulmonary congestion. The aortic arch was within normal limits. An electrocardiogram demonstrated the pattern of left bundle-branch block with sinus rhythm. Examination of the urine was negative. The blood count was normal. The blood Wassermann reaction was negative.

The patient was placed on 0.5 gm. of Diamox daily, 0.25 mg. of Digoxin twice a day and a diet containing 2 gm. of salt. He was seen 1 week later, when he stated that he felt much better and had no dyspnea on walking. The edema of the extremities had completely subsided. The liver edge was no longer palpable, and the lungs were clear. He had lost 8 pounds in weight during the 1st week of therapy, and there was no evidence of peripheral edema or hepatomegaly. He was able to return to work as a store clerk for the first time in 6 months.

Discussion

Thirteen patients with congestive heart failure, treated on the usual regimen of digitalis, low-salt diet and mercurial injections, were subjected to a trial of Diamox by mouth instead of the mercurial diuretics. Diamox was found to have definite diuretic properties in all these cases. In case 1 there was a loss of 4 pounds after twenty-four hours' treatment. In Case 3 the patient lost 10 pounds in the first seven days. In Case 6, there was a loss of 6 pounds after the first week of treatment. In Case 8, the patient lost 4 pounds of weight after the first two days of therapy. In Case 11 the patient lost 6 pounds after the first week of treatment. In Case 12 the patient lost 5 pounds in four days after treatment with Diamox was started. The patients in Cases 9 and 10 had severe cardiac disease, obviously Class 4, despite all therapy, before the Diamox trial. The only beneficial effect in these 2 cases was the less frequent need for Mercuhydrin injections with their associated toxic effects of nausea, vomiting and extreme debility, which occurred invariably after each injection. It was further noted that Diamox alone or in combination with mercurial injections had little diuretic effect in the presence of anasarca and renal decompensation. However, after removal of ascitic fluid, the effectiveness of Diamox appeared to be increased, although supplementary mercurial injections were required. The intervals between injections were notably increased in Case 10 after abdominal paracentesis.

Cases 1, 2, 3, 4, 5, 7, 8 and 12 were enabled to dispense with mercurial injections completely. One patient (Case 13), who had never received mercurial diuretics, responded well to Diamox.

Toxic effects from Diamox consisted of a sense of numbness and pins and needles in the face and extremities, and moderate to extreme drowsiness. These symptoms were encountered in all cases in which the daily dose was 1 gm. or more. However, after this dose had been reduced to 0.5 gm. daily, these symptoms became minimal. In Cases 1 and 8 the dose of Diamox was reduced to 0.25 gm. a day, without alteration in the effectiveness of the drug. In these cases the symptoms noted disappeared entirely. The patients took the daily dose in a single tablet on arising each morning. In view of the satisfactory results with this dose, it would be interesting to learn whether 0.25 gm. daily might not be an adequate starting and maintenance dose. (Friedberg et al.[6] recently observed the most effective dosage schedule in a series of 26 patients with congestive heart failure to be 0.25 gm. three times a day for two days, with courses repeated every two to seven days, or 0.25 gm. once daily, administered continuously.) There were no skin manifestations from the drug. No changes were reflected in the blood counts or urine, suggesting any hematopoietic or renal toxicity from Diamox.

Summary and Conclusions

The action of a new diuretic drug, Diamox, was observed in 13 cases of congestive heart failure. Its action is that of a specific inhibitor of carbonic anhydrase, resulting in the renal loss of bicarbonate, sodium, potassium and water. No serious toxic effects were noted with a dose of 0.5 gm. a day. Eleven of the thirteen patients were kept edema free, with more or less constant weight, on this dose, together with a low-salt diet and Digoxin.

This series is obviously too small to justify any final conclusions. However, it would be interesting to continue observing the effectiveness of this drug in larger groups of patients, and also to determine the factors involved in the refractoriness of patients with renal decompensation.

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MEDICAL PROGRESS

MANAGEMENT OF ACUTE GLOMERULONEPHRITIS*

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RECENT advances in knowledge and understanding of the nature and functional disturbances of acute glomerulonephritis have led to the development of more rational and effective therapy. The purpose of this communication is to review this progress.

ETIOLOGY

The etiology of the condition is unknown. However, considerable information is available regarding the temporal and possibly causal relations between infection with beta-hemolytic streptococci and the onset of acute glomerulonephritis.[1-6] The interval of a few days to four weeks between the streptococcal infection and the onset of acute glomerulonephritis probably represents the time during which immunologic reactions develop that may in some manner participate in the pathogenesis of the renal disorder. Many investigators have attempted to establish the nature of the basic immunologic mechanisms. Serum complement is depressed in many cases; this may be the result of the combination of antigen and antibody.[7, 8] Janeway[2] postulated that the original streptococcal infection produces an antigenic response followed by antibody development and that the antigen-antibody reaction is damaging to the kidney and, perhaps at times, to the entire vascular system.

It has been assumed by Cavelti[9] that some product of the hemolytic streptococcus renders renal tissue itself antigenic, with subsequent formation of autoantibodies to kidney; later these autoantibodies react with normal kidney to produce acute glomerulonephritis. Circulating antibodies to human kidney have actually been demonstrated in cases of acute and chronic glomerulonephritis by Lange et al.[10]

Although hypersensitivity to streptococcic protein is thought by many to be of primary etiologic importance in the pathogenesis,[1, 2, 11, 12] the nature of the basic mechanism must await further clarification. The occurrence of rheumatic fever[13] and Schönlein–Henoch purpura[14] in a small percentage of cases of acute glomerulonephritis suggests that the etiologic factors in all these diseases may be similar in some cases.

The factors responsible for susceptibility to the disease are unknown. No data are available to explain why some patients with recurrent streptococcal infections of the upper respiratory tract do not develop acute glomerulonephritis whereas others do after one such infection among many. Infection with certain virulent "nephritogenic" strains of streptococci in susceptible patients may explain this clinical observation.

It is of great interest that patients with healed acute glomerulonephritis are remarkably resistant to second attacks; the nature of this immunity is not known.[15]

Important studies of the influence of penicillin treatment of acute streptococcal infections on the subsequent development of glomerulonephritis have recently been reported.[4, 5] Weinstein et al.,[4] in a study of 167 patients with scarlet fever (150 children and 17 adults), of whom 127 were treated with 120,000 units of penicillin parenterally per day for ten days and the remainder were given the antibiotic orally, found that 6 patients (5 children and 1 adult), or 3.5 per cent, gave clinical or laboratory evidence, or both, of acute glomerulonephritis eighteen to twenty-five days after the onset of the streptococcal pharyngitis. In 4 cases, penicillin was given within twenty-four hours of the first manifestations of streptococcal pharyngitis, and in 2 antibiotic therapy was not begun until the sore throat had been present for about forty-eight hours. Two thirds of their patients who subsequently developed glomerulonephritis were treated for the initial streptococcal infection within twenty-four hours of the time when it first became clinically apparent. Bengtsson and Birke,[5] in a study of 1100 cases of streptococcal tonsillitis (754 children and 346 adults), most of whom were treated with parenteral injections of 300,000 units of procaine penicillin a day for one week, the others being given the antibiotic orally, reported that in 19 patients (6 children and 13 adults), or 1.7 per cent, acute nephritis developed as a late complication. The interval between the onset of the sore throat and the initiation of antibiotic therapy was not mentioned.

Both groups of investigators commented on the almost complete elimination of the suppurative or bacterial complications of streptococcal infections after the initiation of penicillin therapy. They emphasized the fact that an important group of sequelae, including acute glomerulonephritis, do not appear to be the direct result of bacterial invasion, but are produced after a latent period by a mechanism as yet unknown.

Perhaps sensitization in susceptible patients takes place so rapidly that the eradication of the bacteria even early in the acute phase of streptococcal infec-

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tion occurs too late to prevent the initiation of the mechanisms that are responsible for acute glomerulonephritis. However, in a series of 2000 patients with scarlet fever who received no antibacterial therapy, Weinstein et al.[4] reported that the incidence of glomerulonephritis was about 1 per cent. From their observations and those of Bengtsson and Birke,[5] it appears that the early treatment of streptococcal pharyngitis with penicillin does not appreciably reduce the incidence of glomerulonephritis as a "late" complication.

Weinstein and his associates[4] questioned the role of an allergic mechanism in the development of "late" poststreptococcal complications since little or no antibody response occurred in their penicillin-treated patients.

Rammelkamp[16] recently reported that most of the patients he studied in initial attacks of glomerulonephritis yielded Type 12 streptococci in throat cultures. Studies by others[17, 18] have indicated that strains of Types 2, 4, 18 and 31 may likewise produce nephritis. Rammelkamp concluded that "treatment of acute streptococcal infections caused by nephritogenic strains with adequate doses of penicillin will completely prevent the onset of acute nephritis," [19] a conclusion contrary to that of others described above. Moreover, Weinstein et al.[4] have emphasized the fact that glomerulonephritis may appear mainly with urinary abnormalities and without striking clinical manifestations; the need for careful follow-up studies of acute streptococcal infections after antibiotic treatment is discontinued is evident, even though there is no overt evidence of nephritis. Failure to examine the urine frequently for several weeks after the acute streptococcal infection may cause one to overlook relatively mild cases of glomerulonephritis. As Leiter[20] and Derow[21] have pointed out, such incidents may account for the cases discovered years later without a history of an initial overt attack of glomerulonephritis.

Pathology

Current concepts of the renal pathology have been presented in the excellent monographs by Bell[22] and Allen.[23] The histologic picture varies considerably but consists essentially of a diffuse capillaritis of the glomerular loops that may cause swelling, hyperchromatism and proliferation of the fixed cellular elements; thickening, reduplication and granular fibrinoid alteration of the capillary basement membrane with or without glomerular thromboses; the accumulation of polymorphonuclear leukocytes, both intravascularly and extravascularly; gnarled distortion of the glomerular capillaries; and, finally, a combination of any of these changes.

There is no direct correlation between the degrees of change in glomeruli and tubules; the epithelium of the tubules may be unaltered, notwithstanding acute changes in the glomeruli. On the other hand, the tubular epithelium, especially that of the proximal nephron, may be vacuolated with lipid or fluid, may contain huge hyaline granules or may be so necrotic as to suggest a primary necrotizing tubular disease. The individual histologic types of acute glomerulonephritis are beautifully illustrated and carefully described by Allen.[23] The histologic picture of acute glomerulonephritis may disappear with clinical recovery.

Pathogenesis and Pathological Physiology

Vasoconstriction

Many years ago, Volhard[24] presented a hypothesis of the pathogenesis of acute glomerulonephritis as follows:

> For the understanding of the dangers it is important to bear in mind that the true process consists in a general and also a renal vasoconstriction. Thus in the acute stages we are dealing with a functional condition which endangers not only the kidney but also the other organs especially the central nervous system and greatly threatens the heart. In the acute stage it is the danger to the heart which is of first and highest importance. The danger to the brain is second and to the kidneys only third. The danger that the functional condition in the kidneys will lead to lasting and irreparable changes increases with the degree and duration of the general vasoconstriction manifesting itself by hypertension. The hypertension caused by spastic narrowing of the small peripheral arteries may set in suddenly, even overnight.

Vasoconstriction cannot be accepted as the mechanism of the renal changes in view of the findings of many investigators employing clearance technics that the renal plasma flow, even in the presence of severe glomerular damage, is approximately normal. In fact, in early acute glomerulonephritis the renal plasma flow may be greater than normal.[11, 25, 26] Bradley[27] also found no correlation between changes in renal blood flow and the appearance of elevated blood pressure and concluded that renal ischemia was not a factor in the hypertension.

Although generalized vasoconstriction may occur and may exacerbate the elevated blood pressure, the mechanisms involved are unknown.

Edema

Acute glomerulonephritis has been considered[3] as part of a generalized capillary disease. The fact that edema appears early in the disease and sometimes almost simultaneously with the albuminuria, may precede the albuminuria, or may even occur with hypertension in the absence of albuminuria favors such a view. Furthermore, the high protein content (over 1 per cent) of edema fluid in acute glomerulonephritis was thought to be due to capillary injury, with resultant increase in permeability.[28] On the other hand, Warren and Stead[29] found the protein content of edema fluid to be insignificantly different from that in congestive heart failure. They thought that the few high figures previously reported[28] resulted from contamination with plasma. They also pointed out that it was difficult to reconcile the theory of increased capillary permeability with the observed increase in blood volume. Al-

though the findings of Warren and Stead suggest that capillary permeability is not increased in acute glomerulonephritis, Bradley[11] believes that they do not constitute conclusive evidence since small samples of fluid were taken from areas of gross edema and may not have been representative of edema fluid in general.

Salt and water retention may account for many of the changes observed.[20, 21] The similarity of many of the clinical phenomena to those observed in cases of carbon tetrachloride nephrosis and in overdosage with DOCA, ACTH and cortisone has been commented upon by Altschule and Zamcheck,[22] Rosenheim,[23] Davies[24] and Friedberg.[24] Increased blood volume, elevated venous pressure, hypertension, cardiac enlargement, pulmonary edema, hydrothorax, ascites, edema, hepatomegaly and electrocardiographic changes may occur in these conditions; the cardiac output and circulation time, however, are normal. Rapid reversibility of these changes with diuresis of sodium and water may be striking. It is noteworthy that the adrenal cortex is not overactive in acute glomerulonephritis.[25]

Glomerulotubular imbalance occurs in some cases of acute glomerulonephritis as a result of decreased glomerular filtration and minimal impairment of tubular reabsorption. As the reduced volume of glomerular filtrate passes slowly down the tubules, more efficient tubular reabsorption of sodium and water back into the blood stream occurs. This contributes to the retention of salt and water.

Heart failure may also play a part in the development of edema in acute glomerulonephritis. Rarely, in cases that begin abruptly with the nephrotic syndrome, severe hypoalbuminemia may further contribute to edema formation.

Renal Function

The disturbances of renal function disclosed by clearance technics were recently summarized by Bradley[27]; in general, the disturbances that occur may be correlated fairly well with the histologic changes. Increased capillary permeability occurs as a result of the capillaritis in the glomeruli, and as a consequence plasma proteins and blood appear in the urine. The occurrence in some cases of a reduction in glomerular filtration rate as measured by inulin or mannitol clearance is attributable to capillary obstruction caused by thickening of the glomerular basement membrane, the endothelial-cell proliferation or the exudation of polymorphonuclear leukocytes. Reduction in glomerular filtration rate is the most sensitive index of change in renal function; it causes azotemia. Tubular functional abnormalities are minimal and are consistent with the usually slight degree of tubular damage. The ability to concentrate urine and to excrete phenolsulfonephthalein at a normal rate is not necessarily impaired.

Cardiovascular Phenomena

Friedberg[24] has recently re-emphasized the important manifestations of cardiovascular disturbance in acute glomerulonephritis — that is, hypertension, cardiac enlargement, electrocardiographic abnormalities and heart failure.

Hypertension of varying severity is observed in many cases. Its cause remains unexplained. The role of hypertension in the development of cardiac enlargement and heart failure is not as clear cut as in that of encephalopathic phenomena. The nature of the circulatory disturbance in the brain through which the hypertension participates in the production of the cerebral symptoms is also unknown. However, Moyer et al.[37] suggested that hypertensive encephalopathy of relatively short duration is not associated with depressed cerebral blood flow and that the changes in cerebral function may be related to high arterial pressure transmitted to the postarteriolar capillaries, with a resulting increase in cerebral-tissue pressure and altered cellular function. However, although cerebral edema is often found at autopsy in patients who die of hypertensive encephalopathy, the brain in others may be pale and bloodless.

Cardiac enlargement frequently appears within the first week or two in acute glomerulonephritis. The enlargement is usually slight, but may be considerable when signs of severe heart failure occur. I have repeatedly observed by serial x-ray examinations the return to normal size of the cardiac shadow with the onset of spontaneous diuresis and the subsidence of the renal disease. No evidence of pericardial effusion has been found at autopsy to account for the enlarged cardiac silhouette seen on x-ray study. Dean[38] reported that cardiac enlargement may persist for many years after acute glomerulonephritis in spite of little or no elevation of blood pressure; however, the possibility that the cardiac enlargement in his 3 cases antedated the nephritis cannot be excluded.

Although the cardiac enlargement in acute glomerulonephritis is usually attributed to the hypertension, it has also been observed in the absence of elevation of the blood pressure.[39, 40, 41] Gore and Saphir[40] stated that it is doubtful whether a presumably normal heart could enlarge to a weight of 500 gm. in ten days (their Case 3) through muscular hypertrophy alone. In their study of 160 cases of acute and subacute glomerulonephritis, 16 patients were found to have cardiac enlargement, and 14 of these presented the signs and symptoms of heart failure. The factor common to all the enlarged hearts in their studies was serous myocarditis of patchy distribution. Such increases of interstitial fluid could increase the weight of the heart appreciably and rapidly. They and other authors[41, 42] suggested that increased capillary permeability was the underlying cause of the serous

myocarditis. However, Christian[43] stated that "in fatal cases on which post-mortem studies had been made no changes have been found in the myocardium of sufficient extent or degree to explain satisfactorily the cardiac condition observed during life." An underlying disorder of the myocardium in acute glomerulonephritis has not been uniformly found to explain the cardiac enlargement.

The role of the expanded blood volume owing to retention of salt and water in acute glomerulonephritis in producing interstitial edema remains to be clarified.

Electrocardiographic abnormalities occur more frequently in acute glomerulonephritis than overt signs of heart failure.[44, 45] Low or inverted T waves in Lead 1 and in the precordial leads are the commonest changes.[44, 46] Such findings have been interpreted by some observers as characteristic of anterior myocardial infarction.[47] These abnormalities disappear with the subsidence of the renal lesion. Interstitial fluid accumulation resulting in electrolyte and other metabolic disturbances may account for the T-wave changes. In cases of DOCA overdosage similar electrocardiographic changes have been observed.[48]

Heart failure, or a syndrome resembling it clinically, is the most frequent complication and the commonest cause of death during the initial stage of acute glomerulonephritis. Since a complex combination of factors may exist in such patients it may be difficult to assess the role of each factor in the pathogenesis of the syndrome. Of the utmost importance is the fact that the clinical features of heart failure may appear in previously healthy persons without a past history of cardiac disease, and that with the onset of diuresis the apparent heart failure often disappears very rapidly as the size of the heart returns to normal.

The possible occurrence of an underlying metabolic disorder of the myocardium that might be of primary importance in the pathogenesis of heart failure in acute glomerulonephritis was discussed above. Davies,[33] on the basis of his studies, stated that the evidence for the view that heart failure in acute nephritis is due to myocardial damage was not convincing.

It is well known that manifestations of heart failure in acute glomerulonephritis may occur without significant hypertension; elevations of the blood pressure may, however, precipitate heart failure. Disturbances of electrolyte balance may result in altered function and decreased efficiency of heart muscle. Bradley[49] stated that although deficient excretion of sodium and water because of the primary renal disease results in an increased blood volume, it is probable that heart failure is rarely, if ever, induced by increase of blood volume; an underlying disorder of the myocardium must be present.

Recently, Davies[33] and Rosenheim[31] suggested that the phenomena of heart failure — that is, hypervolemia, elevated venous pressure, cardiac enlargement, pulmonary congestion and edema — and hypertension in acute glomerulonephritis are similar to those observed in cases of overdosage of DOCA or cortisone. They also stressed the rapid reversibility of the apparent heart failure in these conditions with the onset of diuresis.

The term "heart failure" in acute glomerulonephritis may be misleading since it calls attention to the heart as the cause of the phenomena mentioned above. Actually, the reduction of glomerular filtration owing to the glomerular lesion may result in sodium and water retention, hypervolemia, increased venous pressure, cardiac enlargement, hydrothorax, ascites, edema, dyspnea, orthopnea and attacks of pulmonary edema. In the opinion of Davies[33] the absence of previous history of cardiac damage, the normality of the cardiac output and circulation time, the rapid reversibility of heart failure with spontaneous diuresis, and the usual absence of histologic findings in the myocardium in fatal cases suggest that the heart is not primarily involved and that salt and water retention, with resultant expansion of the blood volume, may be the cause of the apparent heart failure.

Altschule[50] has suggested the term "natrigenic hypervolemia" to characterize the phenomena that resemble heart failure not only in cases of acute glomerulonephritis but also in patients suffering with overdosage of DOCA, ACTH or cortisone; the "central fault" is in the kidneys and not the heart. Friedberg's[34] observations on the occurrence of the clinical syndrome of congestive heart failure as a result of sodium and water retention in cases of carbon tetrachloride nephrosis without evidence of cardiac disease support this concept.

Stead[51] recently made the following statement:

> . . . the only way to tell whether a person with acute glomerulonephritis has heart failure is to determine the arterial-venous oxygen difference across the heart. If this is normal in the presence of a normal oxygen consumption, heart failure is not present, as this disease is not one of those which speeds up the circulation. If the arterial-venous oxygen difference is increased, mechanical heart failure is likely.

The occurrence of cardiac enlargement and acute pulmonary edema with dyspnea suggests the presence of acute heart failure. This clinical impression has to date not been substantiated by the necessary hemodynamic studies; indeed, such studies may not be performed because of the hazards to the patient under the circumstances. The heart failure may well be due to metabolic disturbances that interfere with enzyme systems and normal contractility. The renal factor is undoubtedly of great importance and may indeed be the primary cause of the heart failure.

Obviously, the pathogenesis of the apparent heart failure in acute glomerulonephritis is obscure, and its clarification must await further study.

Oliguria and Anuria

Oliguria (excretion of about 500 cc. or less of urine per day) is usually most marked at the onset of acute glomerulonephritis. The causes are considered to be widespread glomerular obstruction with severe reduction of glomerular filtration, salt and water retention, heart failure and severe vomiting, or a combination of these factors. Anuria may supervene and lead to the death of the patient in uremia. However, many cases of anuria of varying duration have been reported with spontaneous recovery.

Diagnosis

It must be emphasized that the patients with acute glomerulonephritis whom the physician is usually called upon to treat are those who present *overt* phenomena, such as gross hematuria, edema, heart failure, pulmonary edema, hypertension, cerebral phenomena, oliguria and anuria, a few days to four weeks after a streptococcal infection. The diagnosis under such conditions is not difficult.

Fishberg[3] collected from the literature a small number of cases in which albuminuria was absent either entirely or for a considerable time after the other features such as edema and hypertension had appeared. Similar cases have recently been reported.[50-54] The diagnosis in such cases may be difficult.

Many years ago, Leiter[20] and Derow[21] emphasized the significance of knowledge of the latent period between the streptococcal infection and the appearance of the first urinary changes in the diagnosis of *asymptomatic* acute glomerulonephritis; this form of the disease probably comprises the vast majority of all cases. In most cases at least a week and often two weeks elapse before the urine shows albumin and microscopic blood. Common clinical practice includes urinalysis only at the height of the streptococcal infection, when febrile or toxic albuminuria may be present. The physician should also examine the urine a week or two after the subsidence of the acute infectious symptoms. This fact of latency has long been known and recently re-emphasized[4] in cases of postscarlatinal glomerulonephritis, but it has been neglected in the much more important, because vastly more numerous, cases of other upper respiratory infections due to the streptococcus.

The differentiation of an initial attack of glomerulonephritis and an exacerbation of the chronic form of the disease may be impossible unless the antecedent history and findings are known. However, the shorter latent period of one to four days between the streptococcal infection and the exacerbation favors the diagnosis of an exacerbation.[18] There are cases in which only time and continued observation distinguish between the initial episode and exacerbation of the chronic form of the disease.

Prognosis

The prognosis in acute glomerulonephritis is good in general. Fishberg[3] agrees with many observers[1, 42, 55] that of the three possible outcomes — complete recovery, chronicity and death during the acute stage — recovery is much more common than chronicity, and death during the acute stage is exceptional. The large majority of children recover completely; the number of cases that become chronic rises greatly with increasing age at the time of onset.

The mortality in the acute phase is related to the severity of the complications, but the patient who survives severe cardiac, encephalopathic or anuric complications has as good a chance of complete recovery as the one with a milder form of the disease. There is no way to predict at the onset which patients will recover, develop the chronic form or die in the acute stage. Death in the acute stage is usually associated with apparent cardiac failure, hypertensive encephalopathic manifestations or uremia. The development of the nephrotic syndrome during the acute phase is associated with a poor prognosis.[56] Many statistical reports related to the immediate prognosis in acute glomerulonephritis show considerable variation in mortality from no deaths[1, 57] to 9.4 per cent.[42] This difference in mortality may be due to the variation in severity of the disease and the small number of cases in each study.

The ultimate prognosis in patients who do not die during the acute stage is fairly good. Published data agree in showing a better prognosis in children than in adults.[1, 3, 42, 55, 57, 58] Thus, Rudebeck[55] reported that 86.3 per cent of 73 patients between ten and nineteen years of age recovered completely, whereas only 51.4 per cent of 37 patients between forty and forty-nine recovered. Ramberg[58] found that 70 per cent of children and only 47 per cent of adults above twenty-five years of age recovered.

Recovery is recognized by the absence of constant albuminuria and hematuria or the presence only of orthostatic albuminuria.[59] Failure to recognize postnephritic orthostatic albuminuria may be an important source of error in distinguishing recovery from progression to chronicity. Orthostatic albuminuria may persist for long periods and may remain permanently after acute glomerulonephritis.[60] I found 12 patients with orthostatic albuminuria among 42 who had recovered. Seven of these patients were sixteen years of age or younger and the others were thirty, thirty-seven, forty-nine, fifty-seven and fifty-nine years old at the time of onset. Thus, the age at onset of acute glomerulonephritis does not appear to be the determining factor in the orthostatic albuminuria, notwithstanding the fact that the usual form of orthostatic albuminuria occurs in youth to persist for only a few years.

Many observers[6, 15, 20, 21, 61] believe that the majority of patients with acute glomerulonephritis are not seen by a physician because they are

asymptomatic and show only urinary abnormalities If healing fails to occur, these cases may progress to the chronic stage and may present various clinical pictures, one of which is the nephrotic syndrome, which Ellis[62] believes to arise *de novo*. The factors that determine chronicity are unknown.

Treatment

Treatment is largely symptomatic in a disease such as acute glomerulonephritis in which the etiology is unknown and most patients recover. There is no known specific therapy that influences healing of the glomerular lesions and prevents progression from the acute to the chronic form of the disease. However, treatment based on current knowledge of the abnormal physiology of acute glomerulonephritis may be effective in the prevention and management of complications and major symptoms.

Prophylaxis

Since infections due to the beta-hemolytic streptococcus appear to be concerned in some manner with the pathogenesis of acute glomerulonephritis, the prevention of such infections should reduce the incidence of the disease. Under ordinary conditions it is impossible to avoid such infections. However, the widespread use of penicillin during epidemics may reduce the number of cases and carriers of streptococcal infection. Although antibiotic therapy appears to be effective in controlling the initiating streptococcal infection and secondary infections, adequate and early penicillin treatment in scarlet fever and streptococcal infection does not always prevent the development of acute glomerulonephritis.[4-8]

Schedules for penicillin treatment of streptococcal infections were recently presented by the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association.[63]

General Measures

Bed rest. Complete bed rest is essential during the acute attack as long as hypertension, heart failure or edema persists. Although it would be desirable to keep the patients at rest until the urinary abnormalities have disappeared, this procedure is usually not feasible because such findings may persist for many months or even years. However, bed rest is clearly indicated until the urinary abnormalities have become stabilized. The co-operation of the patient is essential during this asymptomatic period and can usually be obtained by adequate reassurance. If the patient is a child of school age, arrangements should be made for a home teacher so that he may continue with his lessons during this time.[6] However, protracted bed rest cannot with certainty be claimed under all conditions to constitute a factor contributing to recovery.[55]

Diet and fluid intake. In the initial stage of acute glomerulonephritis the occurrence of azotemia, edema, hypertension, oliguria and cardiac symptoms constitutes an indication for marked restriction of protein and salt. The "hunger and thirst treatment" of Volhard,[24] formerly widely practiced, is now being supplanted by a diet containing 100 to 150 gm. of carbohydrate, no sodium salts and fluid restriction to the volume excreted by the kidneys, in addition to about 1000 to 1200 cc. lost by insensible perspiration.

A more liberal diet and fluid intake are instituted after disappearance of edema, oliguria and hypertension. Except in the initial phase of the disease, when edema, oliguria, azotemia and hypertension are present, it is doubtful if any benefit results from dietetic restrictions.[55, 64]

No dietary or fluid restrictions are indicated in the milder forms of acute glomerulonephritis manifested by urinary abnormalities but without oliguria, hypertension, edema or azotemia. The development of the nephrotic syndrome early requires that the intake of sodium salts be drastically reduced.

Antibiotic therapy. Reports on the use of penicillin do not show convincing evidence of alteration of the course of the disease.[65] However, antibiotic therapy with penicillin or terramycin should be given to patients with acute glomerulonephritis who continue to suffer with the initial or a new streptococcal infection. This therapy should be approached with caution if oliguria or anuria is present. Reduced glomerular filtration may so retard the excretion of antibiotics that blood levels that are toxic to the patient ensue.[66, 67] The toxic manifestations consist of convulsive seizures, rapidly progressive azotemia and sudden death.

Antihistamine therapy. The suggested use of antihistaminic drugs is based on the possibility of blocking some of the effects of the hypothetical antigen-antibody reaction responsible for the development of the disease.[30] The results with such antihistaminic therapy are not impressive,[68, 69] especially in view of the tendency for spontaneous recovery from the disease in the majority of patients.

ACTH and cortisone therapy. Investigations[70-74] on the possible beneficial effects of ACTH and cortisone in acute glomerulonephritis in which a hypersensitivity reaction may play an etiologic role have revealed that these steroids do not significantly alter the natural course of the disease. The evaluation of such therapy is especially difficult since the majority of patients recover spontaneously and often rapidly.

Specific Problems

In a small number of obviously severe cases the development of apparent heart failure, hypertensive encephalopathy and, in rare cases, anuria constitute emergencies that may result in death. Awareness of these serious complications, their prevention if possible, and their early recognition and manage-

ment make the active treatment of acute glomerulonephritis important.

Volhard[24] and others[3, 6, 48] have emphasized the fact that in the acute stage, the danger to the circulation is of primary importance, that to the brain second, and that to the kidneys only third.

Heart failure. Signs and symptoms of heart failure may mask the clinical picture to such an extent that the underlying renal condition may be overlooked. On the other hand, these manifestations may develop during the initial stage of the disease. This syndrome is the commonest cause of death in acute glomerulonephritis.

The knowledge that the several pathogenetic factors are present to produce or simulate heart failure should emphasize the importance of complete bed rest. In addition, the added strain of exercise or the increase of blood volume by intravenous infusions may be sufficient to precipitate the syndrome. If hypertension is present, sudden severe rises in blood pressure may precipitate acute pulmonary edema and death.

Heart failure may be characterized by a sudden onset of dyspnea and orthopnea, often progressing to severe acute pulmonary edema. A rising pulse rate, hacking cough, orthopnea, slight cyanosis and basal pulmonary rales constitute evidence of cardiac failure. Heart failure may develop more insidiously and may involve the systemic as well as the pulmonary circulation. Pleural effusion is common and is part of the generalized anasarca.[58]

In cases of apparent heart failure, sodium intake should be avoided, and fluids should be restricted to 500 to 800 cc. of sweetened weak tea or sugar water. In the presence of impending or actual pulmonary edema, rapid venesection — 500 cc. of blood in adults, and proportionate amounts in children — should be done.

The rapid subsidence of the signs and symptoms of severe heart failure without the benefit of digitalis in these cases leaves the impression that the improvement is due to the spontaneous diuresis rather than changes in contractility of the heart. The possibility also arises that the spontaneous diuresis signifies recovery from capillary and metabolic derangements. Although digitalis in a rapidly excreted form (such as Cedilanid and Digoxin) is recommended by some authors[39, 61] by the oral or intravenous route, depending upon the urgency for the treatment of heart failure in acute glomerulonephritis, it is difficult to evaluate its effect.

In addition to venesection, early administration of oxygen by tent or positive-pressure mask and antifoaming agents[75] should be employed in the treatment of severe pulmonary edema. Morphine and atropine in adequate doses should also be given. Tourniquets on all four extremities may be employed. Tilting of the patient's head below the edge of the bed may relieve respiration by providing drainage of the pulmonary edema. At times, the suddenness and rapidity with which pulmonary edema develops preclude the use of any therapeutic measure to prevent death.

Hypertensive crises. Frequent, careful determinations of blood pressure should be made in all cases of acute glomerulonephritis, especially if hypertension is present. However, not all patients who have an elevated blood pressure have hypertensive complications. The gradual or sudden rise of the blood pressure provides objective evidence of the imminence of heart failure or convulsions or both.

In spite of the fact that the pathogenesis of heart failure in acute glomerulonephritis remains to be clarified, the development of severe hypertension may either precipitate heart failure or aggravate already existing failure. The reduction of the blood pressure to normal levels will at least serve to eliminate the hypertensive factor in the genesis of the heart failure. Often, the return of the blood pressure to normal levels appears to contribute favorably to the patient's recovery from the heart failure.

The physician should be constantly alert to detect the early symptoms of encephalopathy such as headache, nausea, vomiting, irritability or apathy, drowsiness, transient paralyses or visual disturbances; these symptoms of rise of blood pressure are not necessarily accompanied by oliguria or renal insufficiency.

The dosage and frequency of administration of vasodepressor preparations depend upon the degree and duration of the hypotensive effect, the relief of the cardiac or encephalopathic symptoms, and avoidance of toxic manifestations, including severe hypotensive collapse; dosage of vasodepressor medication must be individualized to obtain satisfactory results.

Magnesium sulfate, first introduced by Blackfan and Mills,[76] is often effective in reducing the blood pressure. The studies of Winkler et al.[77] indicate that the desired vasodepressor effect is not obtained until the plasma magnesium has risen from the normal level of approximately 1.5 milliequiv. to 5 milliequiv. per liter. As the blood concentration approaches 10 milliequiv. per liter the tendon reflexes diminish. Respirations are not suppressed until the concentration has risen to between 10 and 15 milliequiv. per liter. If cerebral symptoms develop in the presence of mild hypertension, magnesium sulfate should be given intramuscularly in doses of 0.2 cc. of a 50 per cent solution per kilogram of body weight and repeated at four-hour intervals until the diastolic blood pressure falls to normal levels. If the cerebral symptoms become severe with moderate elevation of the blood pressure, 20 cc. of 10 per cent magnesium sulfate may be given very slowly intravenously at intervals of one or two hours. In the presence of an adequate urinary output, it may be difficult to maintain an effective blood level of magnesium. Therefore, larger doses

of the drug may be necessary over a longer period. However, in the presence of oliguria and azotemia, magnesium sulfate may prove to be toxic and may produce slowing of the respiratory rate; 10 cc. or more of 10 per cent calcium gluconate given intravenously is the antidote.

Because of the lack of any blood-pressure-lowering effects of magnesium sulfate in some cases, effective vasodepressor preparations of the *veratrum alkaloids* may be used intramuscularly in mild or moderately severe hypertension, and the intravenous preparations may be used in severe cases, especially in the presence of convulsions.[78-80] Recent studies[80-84] have shown that although a transient decrease in the urinary volume is observed after the injection of veratrum alkaloids, this decrease is more marked when a profound hypotensive effect is produced by large doses of these drugs. Even though the oliguria is usually followed by a marked polyuria, the reduction in function may be detrimental if continued for a prolonged period in the presence of azotemia. Meilman[85] found that the oliguria is accompanied by reduction of the glomerular filtration rate and of sodium and chloride excretion; these phenomena are transient.

Rapid venesection — 500 cc. in adults and proportionate amounts in children — is sometimes effective in lowering the blood pressure. This procedure should not be employed in the presence of anemia.

Sedation is of great importance in these patients because of the usual presence of restlessness, irritability and apprehension. Small doses of phenobarbital are helpful not only in providing relaxation and rest but also in lowering the hypertension. Rectal administration of chloral hydrate or paraldehyde may be beneficial. However, it is sometimes necessary to resort to such drugs as Sodium Amytal in doses of 0.25 gm. given intramuscularly or intravenously.

Anuria. There is no reliable method of treatment for freeing the obstructed glomeruli to initiate glomerular filtration. Diuretics are of no value, and in fact may be harmful.

Certain principles of treatment[86-90] should be followed in the management of anuria in acute glomerulonephritis, such as the replacement of extrarenal fluid and electrolyte loss, the avoidance of overhydration, the reduction of protein catabolism to a minimum so that the rate of accumulation of toxic end products of protein catabolism is reduced, the avoidance of infection and the removal of metabolites usually excreted by the kidneys. With such a therapeutic regimen, one may anticipate in most uncomplicated cases that urine flow will be re-established within a few days to a week or two as a result of the spontaneous resolution of the capillaritis of the glomeruli.

The possibility of ureteral obstruction is of such paramount importance in patients with anuria that retrograde investigation by a skilled urologist is usually indicated.

Of the greatest value in the management of an anuric patient are adequate laboratory facilities to provide frequent measurements of blood nonprotein nitrogen, carbon dioxide combining power and sodium, chloride and potassium levels. The correct regulation of electrolyte metabolism may be accomplished only if such facilities are available and the measurements intelligently applied.

During the anuric period, fluids should be restricted to the amount calculated to replace the insensible loss, with additional allowance for losses due to fever, vomiting or diarrhea.[91] The fluid intake should not exceed 800 cc. or maximally 1000 cc. Since fruit juices are generally high in potassium content,[92] such fluids should be avoided. Weak tea with sugar or sugar water may be used instead.

It is generally accepted that if only fluids and no calories are provided during the anuric period, protein of the body cells will be utilized to furnish calories. To reduce the excessive catabolism of protein that precedes the liberation of potassium, phosphate and products of protein breakdown, a high-calorie diet, rich in carbohydrate and low in potassium, should be furnished.[93] Borst[94] applied this principle by feeding anuric patients butter and sugar, but this mixture is unsavory and often nauseating. Bull et al.[95] modified this plan of treatment by using a glucose, peanut oil and water emulsion, which is given daily by continuous intragastric drip by means of a plastic intranasal catheter. Fat emulsions for oral administration have recently been developed[96, 97] and are available under the trade names of LipoMul-Oral and Ediol; they may also be given through a nasal catheter.

The use of a potassium-free ion-exchange resin in ammonium form for preventing or reducing dangerous levels of hyperpotassemia has been reported by Elkinton and his associates.[98] Large amounts of potassium may be removed in several hours by intestinal lavage.[99, 100] Frequent determinations of the potassium content of the serum should be done to avoid hypopotassemia.

The acidosis that develops during anuria may be combated by slowly administered intravenous infusions of sixth molar sodium lactate solution in amounts calculated to replace the deficit of base in the extracellular fluid. According to Mudge and Vislocky,[101] part of the sodium given is lost to the cells; when additional amounts of sodium are administered, pulmonary edema may be produced.

Transfusions of packed cells may be given if anemia is present during the anuric period. Sodium citrate that is introduced with the red cells may help to reduce the acidosis. On the other hand, the untoward effects of sodium should always be kept in mind.

Antibiotic therapy should be used to prevent and treat infections that promote protein breakdown

during the anuric period. This therapy should be undertaken with caution because the excretion of antibiotics may be delayed to such a degree that blood levels toxic to the patient ensue.[66, 67] Penicillin and terramycin may be given in smaller amounts at less frequent intervals.

It should be emphasized that since all drugs may be dangerous in the presence of anuria because of reduced excretion, extreme care should be exercised in the administration of all medications.

In summary, the management of the anuric patient with acute glomerulonephritis requires strict regulation of water and sodium chloride intake, a potassium-free diet of high sugar and fat content to spare protein, appropriate antibiotic therapy, transfusions of packed cells for anemia, and measures to prevent and reduce hyperpotassemia and acidosis. If these measures are applied wisely at the onset of anuria as well as during the period of severe oliguria, most patients with reversible glomerular lesions will recover.[61, 90]

Merrill[102] recently stated, "in no given case can one predict when diuresis will supervene, nor can one obviate, even with the best conservative therapy, the possible lethal complications such as acute spontaneous potassium intoxication, et cetera. . . . In competent hands, the artificial kidney may be of value when applied at the proper time in such cases." However, patients whose anuria is associated with acute glomerulonephritis may fail to do well in spite of excellent chemical results after dialysis. In some such patients, convulsions, heart failure and exacerbations of the hypertension have followed this procedure.[102] The necessary heparinization during dialysis represents a calculated risk because of the possibility of initiation of bleeding into the gastrointestinal tract and central nervous system.[104] At any rate, the use of the artificial kidney should be undertaken in acute glomerulonephritis only when the chemical derangements — that is, severe potassemia and acidosis — seriously threaten the life of the patient.[103, 104]

Snapper[92] has recently reported that since lack of detoxification and oxidation of toxic substances during anuria continues, successful removal of dialyzable toxic products by the use of the artificial kidney may not be sufficient to save the life of the anuric patient.

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MEDICAL INTELLIGENCE

ANAPHYLACTOID REACTION TO SODIUM DEHYDROCHOLATE*

Report of a Case

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AUGUSTA, GEORGIA

BECAUSE few reactions to the administration of sodium dehydrocholate (Decholin) in the determination of the circulation time have been reported, only 1 of which was of an anaphylactoid nature, the following case is considered worthy of report.

CASE REPORT

A 64-year-old Negress was admitted to the hospital on July 22, 1952, with complaints of pain, swelling and ulceration of the left leg of 4 days' duration, shortness of breath for some months and dizziness for many years. She had been treated with radium insertion in this hospital for cancer of the cervix on several previous admissions, having received a total of 5000 milligram hours of radium. She had had hypertension for 2 years. There was no past history of asthma or other allergic manifestations.

Physical examination revealed a well developed, fairly well nourished woman in moderate respiratory difficulty. Grade 2 hypertensive retinal changes were present. Crepitant rales were audible in both lung fields, especially at the bases. The heart was enlarged, the border of dullness extending to the left anterior axillary line; the rhythm was regular, and there was a Grade 2 systolic murmur at the mitral area. The abdomen was distended; the liver edge was palpable and tender 3 cm. below the right costal margin. There was edema of both legs, with a hot, red, tender cellulitis extending up the left leg almost to the knee, with calf tenderness on that side. There was a 2-cm. ulcer on the dorsum of the left foot.

Clinical diagnoses were hypertensive cardiovascular disease, congestive heart failure, carcinoma of the cervix, Grade 3, and cellulitis of the left leg.

The temperature was 99.6°F., the pulse 88, and the respirations 20. The blood pressure was 220/90.

At 5:30 p.m. on the day of admission the patient was given 0.8 mg. of lanatoside C intravenously and 0.8 mg. intramuscularly. At 6:55 she was given 5 cc. of 20 per cent solution of sodium dehydrocholate intravenously for determination of the circulation time. There was immediate shortness of breath, cyanosis, pallor and profuse sweating, with a rapid, weak pulse. At the time that reaction was noted the blood pressure was 115/55, later dropping to 90/50. It is of interest that the circulatory collapse was so severe and acute that the usual end point was not obtained.

Neo-synephrine, 1 mg., was given intravenously, with only transient response. This was followed by 1000 cc. of 5 per cent glucose in distilled water with 5 mg. of Neo-synephrine. To maintain a blood pressure of only 100/60 it was necessary to inject 1 mg. of Neo-synephrine into the infusion tubing 3 times in the first 10 minutes. After the first 10 minutes 500 cc. of 6 per cent Dextran was given under pressure, and this brought the blood pressure up to 150/80. Aminophylline, 500 mg., was given intravenously without noticeable effect on the pulmonary edema. Oxygen was started by nasal catheter, being bubbled through 70 per cent alcohol at a rate of 7 liters per minute,[1] with subsequent clearing of much of the pulmonary edema. Wyamine, 15 mg., was given intravenously to maintain the blood pressure, which had varied from 90/60 to 130/70; about 30 minutes later an additional 15 mg. was given subcutaneously, the pressure being maintained at 160/80. The patient had apparently recovered from the initial reaction, and congestive heart failure was well controlled with digitalis and mercurial diuretics. During the following 8 days progressive anemia developed, and there was a steady rise in the nonprotein nitrogen from an initial level of 54 mg. to 131 mg. per 100 cc. terminally. The patient died on the 8th hospital day. Permission for post-mortem examination was not obtained.

Final clinical diagnoses were uremia, hypertensive cardiovascular disease, congestive heart failure, compensated, and carcinoma of the cervix, Grade 3, radium treated.

TABLE 1. *Reactions to Intravenous Use of Sodium Dehydrocholate.*

AUTHOR	HISTORY OF ALLERGY	AGE OF PATIENT yr.	SEX OF PATIENT	TYPE OF REACTION	REMARKS
Norman[4]	Negative	75	M	Anaphylactoid; unconsciousness; rapid pulse, sweating.	Prompt response to caffein, sodium benzoate and epinephrine
	Negative	42	M	Violent asthma	Prompt relief by epinephrine
	Negative	64	M	Diffuse giant urticaria	Prompt relief by antihistamine
Suckle[5]	Negative	52	M	Urticaria	Relief by epinephrine and antihistamine
Coggins et al. (present case)	Negative	64	F	Severe circulatory collapse	Delayed response to efforts to support circulation

DISCUSSION

Since its introduction in 1931,[2] sodium dehydrocholate has been used almost universally as a method of determination of circulation time. In 1941 it was reported to be the least toxic of all the bile salts, and was thought to be well suited for this purpose.[3]

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In the twenty-two years since its introduction only 4 cases of untoward reaction to its intravenous use appear to have been reported. In only 1 of these was the reaction anaphylactoid (Table 1).

Both Norman[4] and Suckle[5] assume that these reactions are due to allergy, although in their cases there was no prior history of allergy. We are unable to account for the phenomenon in our patient on an allergic basis because of both the lack of previous administration of sodium dehydrocholate and the absence of allergic manifestations. A condition of cross sensitization, with haptene formation, or a mechanism of the so-called "speed shock" might be postulated, but that is beyond the scope of this report.

Calcium gluconate may well be substituted for sodium dehydrocholate in the routine determination of circulation time. The end point, unfortunately, remains subjective, but it is of equal accuracy. The one possible contraindication to the use of calcium gluconate consists of patients who have been receiving digitalis or its glucosides.[6]

Summary and Conclusions

A case of severe anaphylactoid reaction to sodium dehydrocholate (Decholin) as used for determination of the circulation time is reported.

Four cases of reaction, 1 anaphylactoid, reported in the literature are briefly reviewed.

Although rare, severe reactions to this drug may occur, and the determination of the circulation time by sodium dehydrocholate in patients with a history of allergy should be abandoned in favor of calcium gluconate.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39301

PRESENTATION OF CASE

A fifty-eight-year-old man was brought to the Emergency Ward because he had been in coma for twenty hours.

For the two years before admission the patient's behavior had been "peculiar." He was forgetful, and at times dazed and lethargic. During the past six weeks he was unable to concentrate at work, was increasingly forgetful and lurched when walking. The family were certain of a definite change in personality, ability to concentrate and clumsiness on performing simple tasks six weeks before entry. At about that time he had a "fainting spell." He was admitted to another hospital, where a diagnosis of "uremia" was said to have been made. His abnormal mental status and his clumsiness persisted throughout hospitalization. He returned home three weeks later, and carried on a fairly normal existence, adhering to a low-sodium diet. On the afternoon of the day before admission he was unusually "unco-ordinated" as well as drowsy and slightly confused. His only complaint was of a "lightheaded sensation." He vomited several times, and a physician, who was called, treated him with one ampoule of phenobarbital intravenously. Shortly after this his speech became slurred and he vomited once, and thirty minutes later he became unresponsive. He had no convulsions but minor twitchings, which the informant was unable to localize. There was no history of injury, fall or other neurologic complaint.

About seventeen years before admission the patient had an episode of chills, fever and dysuria, and was told he had a "kidney infection." Apparently, this persisted despite treatment. One year later he was admitted to the hospital because of fecaluria, and was subsequently found to have a vesicosigmoidal fistula secondary to diverticulitis, for which repair of the fistula and resection of the sigmoid colon were carried out. Two years later the blood pressure was 174 systolic, 120 diastolic. The urine was loaded with white cells and intermittently yielded positive cultures of enterococci, alpha-hemolytic streptococci and *Staphylococcus aureus*. The nonprotein nitrogen was normal. Intravenous pyelograms revealed slight dilatation of both pelves. The patient was followed in the clinic, where blood pressures as low as 140 systolic, 100 diastolic, were recorded. Eight and a half years before admission he came to the hospital because of intermittent claudication of the left leg and on examination was found to be cyanotic. Examination of the blood showed a red-cell count of 5,270,000, with a hemoglobin of 16.1 gm. per 100 cc., and a hematocrit of 52 per cent. He was treated by bimonthly phlebotomies for four or five months. Because of increased arterial insufficiency of the left leg, a left lumbar sympathectomy was performed, with improvement of the leg. During the next six years, he returned because of intermittent exacerbations of urinary infection and prostatitis, which responded to massage and chemotherapy. Five months before admission, he returned complaining of dysuria and low backache, but also had an acid taste in his mouth, constipation and a "tingling" in the right great toe that, he said, had previously heralded attacks of gout. Significant physical findings then included slight cardiomegaly, a split first aortic sound, and a soft apical systolic murmur. The liver was nontender, but the edge was palpable one fingerbreadth below the right costal margin. The blood pressure at that time was 190 systolic, 114 diastolic. The urine had a specific gravity of 1.012 and gave a ++ test for albumin. The blood hemoglobin was 11.8 gm., the blood uric acid 5.7 mg., and the nonprotein nitrogen 115 mg. per 100 cc. Roentgenograms disclosed an ulcer crater in the distal duodenal bulb and two gallstones. The patient improved on a bland, low-sodium diet, and had been treated by his private physician until his present admission.

Physical examination showed a well developed but thin man. Except for occasional myoclonic jerks of the face, forearm and fingers, limited to the right side, he was unresponsive and had stertorous, Cheyne-Stokes respirations. He swallowed without difficulty. The pupils measured 3 mm. in diameter and reacted sluggishly to light. The eyes were slightly divergent and did not move on change of head position. The corneas were clouded; corneal reflexes were bilaterally equal. There was a mild paresis of the lower left side of the face. The optic disks were well outlined; there were no hemorrhages but only arteriolar spasm. The neck was supple, the chest was clear, and the abdomen and extremities were not remarkable. There were no purposeful limb movements and only slight flexion withdrawal from painful stimuli. The left arm and leg were less responsive to noxious stimuli on ad-

mission and were later noted to be flaccid. In contrast the right side had slightly increased tone and exhibited myoclonic jerks of the face, arm and leg. Deep tendon reflexes showed ++ biceps and triceps jerks bilaterally; the radioulnar jerk was ++ on the right and + on the left. Finger jerks were + bilaterally; abdominal reflexes were absent. The cremasteric reflex was ++ on the right and + on the left. The right knee jerk was more active than the left. The plantar responses were questioned on admission, but the next morning were unequivocally bilaterally extensor.

The temperature was 99.6°F., the pulse 82, and the respirations 18 per minute. The blood pressure was 200 systolic, 110 diastolic.

The urine had a specific gravity of 1.010 and gave a ++++ test for albumin and a green sugar test; the sediment contained 20 to 30 red cells 5 white cells, occasional hyaline and granular casts and 1 white-cell cast per high-power field. Examination of the blood demonstrated a hemoglobin of 10.5 gm. per 100 cc. and a white-cell count of 7200. The nonprotein nitrogen was 106 mg. and the uric acid 9.9 mg. per 100 cc., the blood pH 7.36, and the carbon dioxide 22.0 milliequiv. per liter. On lumbar puncture the initial cerebrospinal fluid pressure was equivalent to 290 mm. of water; the fluid was xanthochromic and contained about 500 red cells per cubic millimeter, many of which were crenated and gave a ++++ Pandy test. An electroencephalogram was consistent with a diffuse bilateral abnormality, greater on the left. An anteroposterior roentgenogram of the skull was normal. The pineal gland was not visualized.

The patient remained in coma for nine days. All extremities became flaccid, and there was no response to painful stimuli. On the fifth hospital day the pupils were fixed; terminally, the right was greater than the left. The pulse was 80, the respirations 25 and regular, and the blood pressure 160 systolic, 90 diastolic. Lumbar puncture at this time yielded clear, slightly xanthochromic spinal fluid under an initial pressure equivalent to 70 mm. and a final pressure equivalent to 60 mm. of water. The fluid contained 120 red cells and 3 lymphocytes per cubic millimeter. The Pandy test was negative. The total protein was 55 mg. per 100 cc. He vomited small amounts of coffee-grounds material, requiring frequent suctioning. On the evening of the ninth hospital day he was found gurgling; his bed was covered with coffee-grounds vomitus. Resuscitation was unsuccessful, and he died a short while later.

Differential Diagnosis

Dr. Raymond D. Adams*: There are a few questions that I should like to ask. Did this man have headaches during the last weeks or months of his illness?

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Dr. Lawrence J. Barrows: There were none.

Dr. Adams: Had he been working until the day he fell ill the last time?

Dr. Gerald S. Foster: He had worked up until the fainting spell for which he went to the other hospital several weeks before admission.

Dr. Adams: Had he been alert and mentally competent after he was discharged from the hospital until his second admission?

Dr. Foster: His sister said that he had been forgetful for a period of two years, but about six weeks before admission, there was a definite change — he became more forgetful and had more difficulty in concentrating but he remained fairly alert and did not complain of headaches.

Dr. Adams: Were renal-function tests done in this hospital?

Dr. David Kahn: A phenolsulfonephthalein test was done.

Dr. Adams: And there was definitely impaired renal function?

Dr. Foster: He had been in uremia for several years.

Dr. Adams: He had a fixed specific gravity. Did the nonprotein nitrogen or blood urea rise during the last hospital admission? Only one nonprotein nitrogen determination was given: 106 mg. per 100 cc. on admission.

Dr. Foster: The nonprotein nitrogen rose to 118 mg. per 100 cc.

Dr. Adams: Was the total protein of the first spinal fluid determined?

Dr. Barrows: The total protein was reported to be 7 gm. per 100 cc., but that was not considered a valid determination because the fluid did not clot and it was thought that the specimen had been contaminated by serum.

Dr. Adams: Was the fluid clearly yellow?

Dr. Foster: It was said to be definitely xanthochromic by the person who examined it.

Dr. Adams: Did the x-ray films show anything?

Dr. Stanley M. Wyman: The skull films are not very informative.

The films of the abdomen show a small right kidney. The left kidney is not as well outlined, but I think it is also shrunken. This twenty-minute film of the pyelogram demonstrates great impairment of renal function. One film taken a couple of years previously had shown more function.

Dr. Adams: It is clear from the clinical data that this man suffered from several diseases, and if we are to succeed in reaching an approximately correct diagnosis we must first decide which of these many symptoms and signs are important. This is often necessary in clinical work — in fact, I observe that one of the best tests of clinical judgment is to have to decide which of many symptoms and signs are relevant to the main clinical problem and which ones may be disregarded.

We are told that this man had had, during the past seventeen years, recurrent "kidney infections," diverticulitis with a vesicosigmoidal fistula for which a portion of the sigmoid was resected, intermittent claudication of the left leg and lumbar sympathectomy, polycythemia for which phlebotomy was done repeatedly, duodenal ulcer, hypertension and gout.

Many of these diagnoses can be questioned because during the previous admission here, when he was comatose, no data concerning these diseases could be obtained. The blood counts, as given, are certainly not sufficient for the diagnosis of polycythemia; in fact, the patient was anemic during the last month of life. Nevertheless, the diagnosis of polycythemia may have been entertained for reasons not given, and an illness such as kidney disease or repeated bleeding could have resulted in the terminal anemia. One hesitates to diagnose gout without some indication of a recurrently painful joint or tophi. The only indication of it was elevated uric acid on the last admission, which can be explained on the basis of renal failure. Duodenal ulcer we must accept on x-ray evidence.

The illnesses that are likely to have been of significance in relation to his death are arteriosclerosis, hypertension and kidney disease. We may assume that intermittent claudication in a fifty-year-old man, effectively treated by sympathectomy was due to atherosclerosis and may suspect that he had this disease in other major vessels such as the aorta and the coronary and cerebral arteries. The numbness of the right great toe may have been due to involvement of the arteries of the leg. Hypertension of fifteen years' standing is likely to have contributed to atheromatous formation in major arteries. One's first inclination is to say that the kidney disease, which caused chills, fever, dysuria, pus and bacteria in the urine, dilated renal pelves, repeated "urinary infection and prostatitis," low-back pain and elevation of nonprotein nitrogen, was chronic recurrent pyelonephritis, and, as clearly pointed out by the clinicopathological studies of Weiss and Parker,[1] hypertension and nephrosclerosis have complicated this condition. It would be surprising for a patient with a nonprotein nitrogen of 115 mg. per 100 cc. to survive for eight and a half years. I assume that this was not uremia but extrarenal azotemia due to some complication such as bleeding from a peptic ulcer as well as impaired renal function.

Dr. Kahn: The nonprotein nitrogen was consistently high in a number of different determinations.

Dr. Adams: It not only was elevated at the time but also remained elevated.

Dr. Walter Bauer: A consistently elevated nonprotein nitrogen is possible if the renal disease is not progressive. We see this on occasions in both arteriosclerotic renal disease and pyelonephritis. An occasional patient may have nonprotein nitrogen levels of 60 to 90 mg. per 100 cc. for several years or more.

Dr. Adams: I did not realize that. On the basis of these data and knowing of the improbability of making a correct diagnosis of the type of kidney disease from the urinary findings, as pointed out by Kenneth Mallory and Ellis,[2] I should favor a diagnosis of chronic recurrent pyelonephritis with impaired renal function and surely would expect to see some type of nephrosclerosis superimposed.

I begin my analysis of the last illness, then, knowing that the patient had hypertension of many years' standing, and that he had severe kidney disease and atherosclerosis. We are informed that he had been undergoing a peculiar change in behavior for the past year. It is stated that he was forgetful, lethargic and unable to concentrate and, further, that his movements were "unco-ordinated" and clumsy, and that he lurched when walking. These may be taken as signs of disordered brain function, and the only problem is whether they can be attributed to the uremia he was said to have had, to some other general metabolic upset or to structural disease of the brain. I favor the last notion because clumsiness and inco-ordination of movements, even though probably slight, are not part of the uremic syndrome.

Finally, the illness that took his life began, it should be noted, on the day before admission to the hospital. Within a few hours he became more "unco-ordinated" and "lightheaded," and vomited several times; his speech was slurred (this after phenobarbital ? 120 mg.), and coma with a flaccid left hemiparesis developed. The coma persisted for nine days until death. The cerebrospinal fluid was under increased pressure and was xanthochromic with a low red-cell count, and, in the second specimen of cerebrospinal fluid, the protein was normal, indicating that the xanthochromia came from bleeding into the ventricle or the subarachnoid space, with the pigment being oxyhemoglobin and bilirubin.

What are the possible causes of a fatal illness that abruptly transforms a man from an alert mental state to coma, causes a hemiplegia and colors his cerebrospinal fluid? I should consider head injury with subdural hematoma or brain contusion, a hemorrhagic infarct from embolism, ruptured aneurysm with subarachnoid or meningocerebral hemorrhage, hemorrhage from a tumor or angioma and finally a brain hemorrhage due to arteriosclerosis and hypertension.

Let us for a few moments review each of these possibilities.

Hemorrhagic softening of the brain from embolism in a brain artery or from venous thrombosis may cause enough subarachnoid hemorrhage to simulate a primary subarachnoid hemorrhage or

produce an unmistakable xanthochromia of the cerebrospinal fluid. I hesitate to diagnose brain infarction because the symptoms developed acutely rather than suddenly, as is usually the case with embolism, and the coma was deep and persistent. Elevation of cerebrospinal-fluid pressure could occur with a massive softening. Thrombosis of venous sinuses or cerebral veins would be difficult to affirm or negate.

Hemorrhage into a pre-existing tumor may on rare occasions cause a rapid onset of coma or hemiplegia, as in the case discussed by Dr. Charles S. Kubik last year.[3] However, there are usually symptoms suggestive of tumor before the apoplectic attack. To diagnose glioma with hemorrhage I should be forced to disregard the other medical diseases that this man had, and that I am unwilling to do.

Saccular aneurysm or vascular malformation may rupture at any age and cause either a primary subarachnoid hemorrhage with headache, stiff neck, nausea and vomiting, or a meningocerebral hemorrhage with the same symptoms and, in addition, hemiplegia or aphasia. Consciousness is altered less than with brain hemorrhage and the cerebrospinal fluid would be, on the second day, grossly bloody. Prolonged coma is, then, against this diagnosis.

Brain trauma. There was no evidence of head injury either by history or physical examination. This probably excludes brain concussion and contusion. There were neurologic symptoms for the last two years, which is a long period even for a chronic subdural hematoma. The latter is often a differential diagnosis, however. The injury that causes it is often overlooked. The lack of headache, the increasing mental dullness and the rapid onset of coma in an otherwise normal person would be unusual in subdural hematoma, and yet a progressive dulling of intellectual functions ending in coma with mild hemiparesis is the usual clinical picture. I cannot make a diagnosis of subdural hematoma, and I exclude it with much uncertainty. When one is presented with this problem clinically the wisest course of action is a temporal burr hole on each side. This offers the patient a chance of recovery from the one treatable disease that he could have.

A spontaneous (nontraumatic) brain hemorrhage due to arteriosclerosis and hypertension is the leading diagnosis in my opinion. I should suggest that it was located in the central part of the right cerebral hemisphere, — in the thalamus and internal capsule or the lenticular nucleus and internal capsule. Furthermore, I should expect it to have been a medium-sized hemorrhage, 3 to 4 cm. in diameter, one surface of which had extended to the wall of the right lateral ventricle, with leakage of a small amount of blood into the cerebrospinal fluid. Extension downward into the midbrain or some secondary hemorrhages in the midbrain could explain the fixed, unequal pupils.

Did the patient die of malignant nephrosclerosis with hypertensive encephalopathy? Probably, he did not. There was no necrotizing retinal arteriolar disease with hemorrhagic exudates and papilledema. The blood pressure was not sufficiently elevated. Uremia could not explain this state because the nonprotein nitrogen had not risen in the last few weeks and was not high, and the carbon dioxide was normal; moreover there were lateralizing signs and the cerebrospinal fluid was yellow. I should expect the pathologist to have found hyalin and hyperplastic arteriolar sclerosis. Coffee-grounds vomitus is a frequent agonal symptom with all serious neurologic diseases that produce coma and will probably be explained by erosions of gastric mucosa rather than frank ulceration. There may have been aspiration of vomitus and aspiration pneumonia, and surely pulmonary congestion, edema and probably bronchopneumonia.

As a guess, I should explain the personality change of the last one or two years on the basis of multiple small foci of ischemic necrosis in the basal ganglions and brain stem.

Dr. Bauer: If you had seen this patient on the ward, Dr. Adams, would you have advised an operation?

Dr. Adams: My inclination, if the facts were exactly as they are described in the record, would probably have been not to have done a burr hole, unless one of our interns said that we should. I am usually persuaded by anyone who has a "feeling" about a subdural hematoma.

Dr. Bauer: I reasoned as you do; however, the majority thought that this patient would survive the burr-hole procedure.

Dr. Adams: Dr. Ballantine, would you put a burr hole in this man?

Dr. H. Thomas Ballantine: I think it would not have taken a great deal of urging for me to have put burr holes in this man with fairly well localized signs, with an increased spinal-fluid pressure, with a low red-cell count in the spinal fluid and with a history of hypertension. I think we should have expected to find a subcortical clot as the result of a rupture of an arteriosclerotic vessel and should have hoped to influence favorably his hospital course by evacuating the subcortical clot.

Clinical Diagnoses

?Cerebral hemorrhage.
?Subdural hematoma.

Dr. Raymond D. Adams' Diagnoses

Cerebral hemorrhage, right thalamus, internal capsule, lenticular nucleus.
Secondary midbrain hemorrhage.
Cerebral atherosclerosis.

Hypertensive and arteriosclerotic vascular disease.
Chronic pyelonephritis.
Benign nephrosclerosis.
Uremia.

Anatomical Diagnoses

Subdural hematoma, right.
Chronic pyelonephritis.
Nephrosclerosis.
Bronchopneumonia.
Cardiac hypertrophy, moderate, hypertensive type.

Pathological Discussion

Dr. Edward P. Richardson, Jr.: On removing the calvarium and inspecting the intact dura mater we observed a pronounced, dark-purplish discoloration of the dura on the right side, the result of an accumulation of blood beneath it. Cutting the dura released a large right-sided subdural hematoma that was made up of an estimated 100 to 150 cc. of semisolid, clotted, brownish-red blood. In thickness the hematoma was maximally about 3 cm. In addition to the semisolidified blood clot there was a smaller quantity of dark-chocolate-brown fluid. The hematoma was not adherent in the slightest to the dura or pia arachnoid and gave no gross evidence of encapsulation.

Dr. Bauer: What is the earliest that encapsulation takes place?

Dr. Adams: The outer capsule begins to form within a few days, and there is a definite membrane within a week. The inner capsule of a sizable subdural hematoma will not appear for ten days to two weeks; even then, it is a very thin membrane. Within six weeks there is a heavy inner membrane.

Dr. Bauer: On the basis of what you have said, would you care to estimate the duration of this subdural hematoma?

Dr. Richardson: The color of the blood was dark reddish brown, and the fluid that was with it was deep brown and contained methemoglobin.

Dr. Adams: I think that would mean it was of weeks' standing rather than of days'.

Dr. Barrows: We thought it was of about a week's duration because of the methemoglobin in the fluid.

Dr. Bauer: Are the findings more consistent with a duration of days or one of weeks?

Dr. Richardson: I should say that it was a matter of days rather than weeks, judging from the absence of any clear membrane formation.

Upon finding the hematoma we looked more carefully at the skull but saw no evidence of a fracture. We did find a small abrasion of the scalp immediately above and behind the right ear and a small extravasation of blood into the temporalis muscle in this region. The hematoma indented the major part of the convex side of the right cerebral hemisphere. There was a right temporal pressure cone, and the structures shifted to the opposite side. Section through the midbrain and upper pons revealed several small hemorrhages in the tegmental areas, such as we often see with a temporal pressure cone. Multiple sections through the brain failed to disclose any intracerebral lesion other than a small cortical contusion on the right superior temporal gyrus posteriorly, approximately under the scalp abrasion.

Dr. Bauer: I do not think the medical service had the benefit of a neuromedical opinion; they did obtain a neurosurgical opinion.

Dr. Adams: It would have to have been better than mine.

Dr. Foster: We had a neuromedical opinion. Dr. Rhett Talbert suggested that this was possibly a subdural hematoma. At that point, when we were prepared to do burr holes, the patient was in such poor condition that the neurosurgical consultant decided that we ought not to proceed with burr holes.

Dr. F. Dennette Adams: Was the trauma the source of the hematoma?

Dr. Richardson: As far as we know it was. There was no reason for assuming that it was not.

Dr. Bauer: Did he have pyelonephritis?

Dr. Kahn: The findings in the remainder of the autopsy were much as Dr. Adams predicted. There was severe chronic kidney disease; the kidneys were small, weighing 180 gm. together, and had coarsely granular surfaces and narrowed cortexes. Microscopically, there was a mixture of severe chronic pyelonephritis and nephrosclerosis so that little normal-appearing renal parenchyma remained. The prostate was moderately enlarged; the bladder showed chronic cystitis; and the ureters were not dilated. There was sigmoid diverticulosis and numerous peritoneal adhesions; the site of the end-to-end anastomosis in the descending colon was negative, and there was no residuum of the vesicocolic fistula. The stomach showed numerous mucosal petechial hemorrhages. There was a severe terminal bronchopneumonia of the aspiration type. The heart was moderately hypertrophied. The bone marrow and spleen were not remarkable.

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CASE 39302

Presentation of Case

A thirty-two-year-old housewife was admitted to the hospital complaining of muddleheadedness and headaches of fifteen years' duration.

At first the headaches were severe but not incapacitating, were usually supraorbital and occipital but occasionally unilateral and occurred with menstruation. They were often preceded by visual scotomas and were accompanied by nausea, fatigue, irritability and mental confusion. She seemed to have difficulty in word selection although enunciation was good. The headaches lasted a few hours to a few days, and as they gradually increased in frequency and severity there seemed to be a relation to stress and emotional tension. Attacks were more common during her college years, just before her marriage and while she was in nurse's training for a short while. On three occasions the headache was preceded by transient loss of control of the left hand, lasting only a few minutes.

Eight years before admission she was seen at another hospital and was found to have a red-cell count of 5,600,000, with a hemoglobin of 19.4 gm. per 100 cc., and a white-cell count of 10,000, with a normal differential. Physical examination was negative except for a moderate, blowing systolic murmur heard in the region of the left scapular angle. There were no cardiac murmurs. There was no cyanosis. A roentgenogram was said to have demonstrated enlarged bronchi in the left lung. Mental confusion and lethargy were almost constant, and she was treated with eight phlebotomies. Six years before entry she was seen at a second hospital, where polycythemia was again found, with red-cell counts ranging from 5,100,000 to 7,000,000. Physical examination was again negative except for a soft systolic murmur along the left sternal border brought on by exercise, but this was not considered significant. X-ray films of skull, sinuses and chest were said to have been normal. During the last eight years she had had about ten episodes of spontaneous severe epistaxis, with loss of approximately 100 cc. of blood on each occasion, which came from the right nostril. Two months before admission three more phlebotomies were performed. She was referred to this hospital for treatment of the polycythemia.

The past and family histories were noncontributory. The patient had 3 children; the youngest was ten months old. All had been born prematurely.

Physical examination showed a well developed and well nourished woman in no distress. There was slight cyanosis of the lips and nail beds. The conjunctivas were slightly suffused. There was minimal clubbing of the fingers. A few small cherry-red spots were present on the skin and tongue. The left lobe of the thyroid gland was diffusely enlarged to approximately one and a half times the normal size. The heart was of normal size. There was a slight increase in the pulmonic second and mitral first sounds, a Grade 1 pulmonic systolic murmur and an apical third sound. There was a Grade 3 systolic bruit over the left lower part of the chest in the posterior axillary line. The rest of the physical examination was negative.

The temperature was 98.6°F., the pulse 80, and the respirations 20. The blood pressure was 140 systolic, 80 diastolic.

Routine stool and urine examinations were negative. Examination of the blood revealed a red-cell count of 6,030,000, with a hemoglobin of 18.2 gm., and a white-cell count of 7200, with 68 per cent neutrophils, 28 per cent lymphocytes and 2 per cent monocytes. There was slight variation in size of the red blood cells. The hematocrit was 50 per cent, and the arterial oxygen saturation

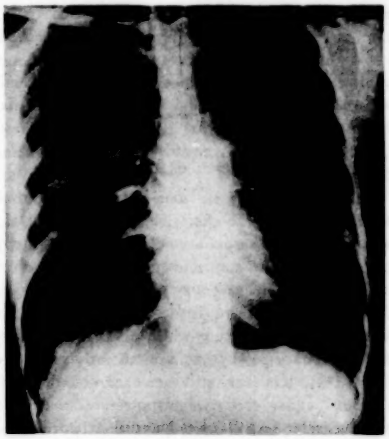

FIGURE 1.

78.5 per cent. The circulation time, arm to tongue, with 5 cc. of Decholin was 15 seconds, with a sharp end point. An electrocardiogram was within normal limits. An electroencephalogram was normal.

A roentgenogram of the chest demonstrated a sharply defined area of increased density, measuring 4 cm. in diameter, lying probably in the lateral segment of the left lower lobe and apparently connected to the hilus of the lung by at least two linear densities, one measuring approximately 1 cm. and the other 1.5 cm. in diameter (Fig. 1). There was apparent diminution of these abnormal findings during the Valsalva maneuver (forced expiration against a closed glottis). The pulmonary markings were more prominent than usual in the right-lower-lung field. Kymographic studies were not informative.

On the eighth hospital day an operation was performed.

Differential Diagnosis

Dr. Robert L. Berg*: In summary this thirty-two-year-old woman, the mother of 3 premature children, at the age of seventeen began to notice muddleheadedness (a not uncommon finding in seventeen-year-old girls) and headaches. She also had occasional loss of control of the hands, which was probably due to anoxia of some sort; polycythemia, without enlargement of the spleen; a murmur over the left posterior axillary line; cyanosis and clubbed fingers; epistaxis and a few small cherry-red spots; a 50 per cent hematocrit, with a much depressed arterial oxygen saturation; and a normal circulation time. In addition she had the intriguing mass in the chest. There is no doubt that the clubbing, cyanosis and polycythemia together suggest a clinical entity, which I shall discuss shortly, but that of the three findings polycythemia is the central and critical problem in the case.

The first point to be considered, even if there were no mass in the chest, is whether or not this was primary or secondary polycythemia. Actually, in either case one may find masses in the chest — in primary polycythemia presumably from old infarcts. When there is no enlargement of the spleen and no immature white cells and no basophilia, primary polycythemia in an early stage may be present, but it is at best a hazardous diagnosis to make under such circumstances. Therefore, I shall consider secondary polycythemia as the most probable diagnosis and consider the reasons for secondary polycythemia. In the presence of a low oxygen saturation of the arterial blood I am forced to the conclusion that this patient had a right-to-left shunt in some portion of the body. For simplicity's sake the right-to-left shunt may be limited to two conditions: she could have had either a patent foramen ovale combined with pulmonary stenosis or hypertension, which forced the blood from right to left, or an aneurysm in the lung between the arterial and venous systems. In the latter there would have been a normal pressure in the right atrium, and the diagnosis in all probability could have been established, even without an x-ray picture, by conclusive evidence of a normal pressure. I do not know what the pressure was but since the x-ray findings were so suggestive it really was unnecessary to expose the patient to cardiac catheterization. May we see the x-ray films now?

Dr. Joseph Hanelin: The x-ray examination of the chest, as Dr. Berg has intimated, is pathognomonic of the situation. This rounded density lies within the lateral portion of the left lower lobe anteriorly, adjacent to the diaphragm; connected with the mass are these two tortuous broad densities, which extend from the lung root (Fig. 1). The lungs otherwise seem normal, and the heart is not enlarged to any degree — it may be borderline in size.

Dr. Berg: Certain of these clinical findings could have been produced by an aneurysm of the pulmonary artery that was intimately connected with the hilus, but it was apparent that this was too far out to be that; do you agree?

Dr. Hanelin: Yes.

Dr. Berg: Could it have been anything but an arteriovenous aneurysm in the lung?

Dr. Hanelin: I do not think we would consider anything else. This is one of the few radiographic appearances that is pathognomonic, and the diagnosis may be made unequivocally.

Dr. Berg: A mass in the lung with polycythemia rubra vera would result from an old infarct and would not have this lobulated appearance or, in all probability, these streaking connections to the hilus.

Dr. Hanelin: It definitely would not have the vessels extending from it to the hilus. An infarct may have a rounded contour, but this will not persist and linear scars are the usual residua.

Dr. Walter Bauer: Would fluoroscopy have been helpful here?

Dr. Hanelin: Yes; with the Valsalva maneuver it was possible to demonstrate diminution in the size of the mass.

Dr. Berg: Did you try the opposite, the Müller experiment?

Dr. Hanelin: We have one film in which the Müller experiment was done; the mass became larger.

Dr. Berg: Did it increase with normal deep inspiration?

Dr. Hanelin: I cannot tell you that.

Dr. Berg: As a matter of fact the decrease of these aneurysms with the Valsalva experiment was the basis of an early suggestion that an artificial pneumothorax might control this disorder, but it

*Assistant physician, Massachusetts General Hospital.

does not work. If air is introduced into the lung cavity, the lung collapses but the aneurysm does not, which is what one might expect when he considers that a pump keeps this balloon constantly inflated.

I might review briefly the probable sequence of events in this patient. In the first place she had the wrong parents. This disorder — anomalous arteriovenous communications — is a hereditary one since it is undoubtedly part of the disease that we refer to by many names, Rendu–Osler–Weber disease — namely, hereditary hemorrhagic telangiectasia. At some primordial stage of embryonic development at a time when the function of small primitive blood vessels changed from a venous to an arterial sort, confusion arose, and some vessels did not differentiate and were left as communications between the arterial and venous sides of the body. These communications were of no importance early in her life but after the growing process had been completed — namely, in the teens or twenties — there was a gradual increase in these communications. Indeed, she had cherry-red spots in the mouth and on the tongue, and she had epistaxis from the right nostril, where one must assume there was a telangiectasis. She may have had two other areas of telangiectasis: the lobe of the thyroid gland, which was enlarged, and the right lower lobe of the lung, whose markings were increased. Gradually, as she grew older, the blood coursing through these short cuts resulted in a decreased arterial saturation of oxygen with increased symptoms of anoxia beginning with muddle-headedness and headache. Such symptoms are common in polycythemia, as are faintness, unconsciousness, weakness, dizziness and convulsions. Later on she temporarily lost control of her hand and had clubbing and cyanosis.

The anoxia may have had one other effect: it may have resulted in some spasms of the arteries of the normal pulmonary tissue that increased slightly the flow of blood to the right atrium and thus forced more blood through the shunt, which in turn would have aggravated the anoxia, increased the resistance and produced a vicious circle. In an elegantly Johns Hopkins' type of paper Dr. Friedlich,* who is now here, presented this formulation two or three years ago; he indicated that in a group of 4 patients of this sort more than 60 per cent of the total blood flow from the right atrium passed through the shunt. One can see, then, why an immense polycythemia is necessary; some patients have as many as 11,000,000 red cells. However even with the decreased resistance in the shunt, there is an increased resistance of the normal pulmonary tissue, and the over-all effect produces no increase in pulmonary resistance. Similarly, the decreased resistance in the shunt does not lead to a reduction in total pulmonary resistance so that there is no increased output of the heart and, generally speaking, no enlargement. One of Dr. Friedlich's patients did have some enlargement of the heart.

A further result of the anoxemia is that the bone marrow produces more red cells and therefore increases the tendency to thrombosis. When one recalls that the word, infarct, means "to stuff up," one can regard this patient's blood vessels as well stuffed — much disposed to thrombosis and infarction. In addition to spasm of pulmonary vessels another cause of increased pulmonary resistance might be widespread small thromboses in the lung. Such small thromboses undoubtedly account for cerebral symptoms in some cases.

It is possible that the polycythemia accounted for the premature birth of the patient's children. There is no mention of prematurity in this type of polycythemia in the literature that I have been able to find; however, it is evident that because the mother had a low arterial oxygen saturation, the fetus would have a low one and undoubtedly an even more profound polycythemia than children normally have at the time of delivery, with an increased tendency to thrombosis and an increased tendency to premature separation of the placenta.

The operation, I assume, was a left lower lobectomy. However, if the x-ray evidence in the right lower lobe was indicative of telangiectasis and a potential aneurysm, one might expect as the shunt was cut off that the total pulmonary resistance would rise with an increased pressure and very probably a ballooning out over a relatively short time of this telangiectasia in the right lower lobe and greater susceptibility to the most dangerous complication of the disease, hemorrhage directly from the aneurysm.

Clinical Diagnosis

Arteriovenous aneurysm, left lower lobe.

*Friedlich, A.L., Bing, R. J., and Blount, S. G., Jr. Physiological studies in congenital heart disease. IX. Circulatory dynamics in anomalies of venous return to heart including arteriovenous fistula. *Bull. Johns Hopkins Hosp.* 86:20-57, 1950.

Dr. Robert L. Berg's Diagnoses

Congenital arteriovenous communication in lung.
Hemorrhagic telangiectasia.

Anatomical Diagnosis

Pulmonary arteriovenous aneurysm, left lower lobe.

Pathological Discussion

Dr. Benjamin Castleman: This patient was operated on by Dr. Gephart, who found a cystic area in the anterior medial segment of the left lower lobe with a number of adhesions between it and the diaphragm. A lobectomy was performed. We injected the pulmonary artery of the specimen with Urokon. This photograph of the x-ray film

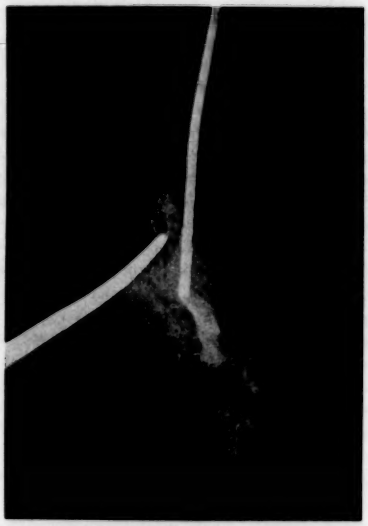

Figure 2.

of the injected specimen shows the artery to the anterior medial segment branching into two segments and entering a cavity (Fig. 2). We continued the injection of the Urokon until the cavity was filled, and the Urokon then entered the venous channel (Fig. 3). In the specimen we found the arteriovenous aneurysm — a trabeculated sac — into which the two branches of the artery and the markedly dilated vein were connected (Fig. 4). Both the artery and vein of the anterior medial segment were almost the same size; the artery was thin and looked more like a vein. The main artery to the left lower lobe was also quite dilated and thinned out and also appeared more like a vein, indicating that the effect of the process had extended beyond the branch to the anteromedial segment.

Dr. F. Thomas Gephart: At operation the artery below the superior-segment branches was so mark-

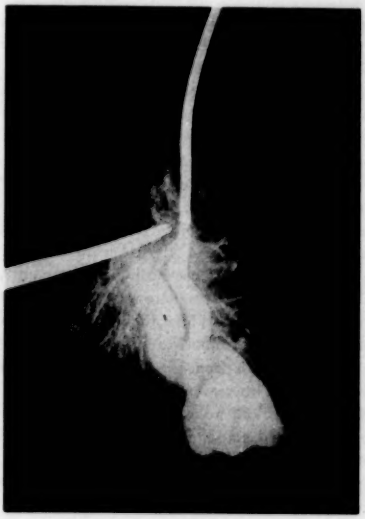

Figure 3.

edly dilated that it did not seem feasible to proceed with anything less than a lobectomy. We had hoped to do a segmental resection. The dilatation seemed to involve all the branches to the basal segments of the lobe, and it seemed unwise to try to preserve the small superior segment above. The operation was quite easy; the fissure was nearly complete and it was simply a matter of ligating the artery and then the vein. There were definite vascular adhesions to the diaphragm only in the region of the fistula. That has been reported in the literature. I do not know why this occurs unless there is some sort of reaction around the fistula itself.

Dr. Castleman: Dr. Hanelin, have you any more to say about the opposite side?

Dr. Hanelin: We have one postoperative film, which I do not believe shows any development of further aneurysmal dilatation.

Dr. Edward F. Bland: Could you identify those vessels now?

DR. HANELIN: Yes; the superior vessel is the artery and the larger inferior channel is the vein. Actually, there was some question in my mind whether there might not be a small arteriovenous communication on the right side. I am not certain of it. In the oblique films there is a 1-cm. density

FIGURE 4. *Pulmonary Arteriovenous Aneurysm.*
The instruments are in the two branches of the pulmonary artery; the dilated pulmonary vein has previously been opened. Both arteries and vein open into the aneurysmal sac.

that may represent an arteriovenous malformation in the right lower lobe.

DR. BAUER: Did you notice it in the lateral view too?

DR. HANELIN: I cannot identify it in the lateral film.

DR. ALLAN L. FRIEDLICH: A good many of these people have multiple lesions, and some who appear to have one single lesion, as this patient did, may have multiple microscopic aneurysms in addition. We are always afraid that there may be another fairly large lesion close to the hilus or hidden by the heart. Angiograms are sometimes done in an attempt to rule out the presence of another such hidden communication. Two hazards that these patients face, in addition to that of exsanguinating hemoptysis, are an increased incidence of brain abscess, presumably due to the right-to-left shunt, and the danger of air embolism to the brain. Since venous blood has access to the arterial circulation one must be particularly careful to avoid even small air emboli during intravenous infusions.

DR. JOHN B. STANBURY: Dr. Berg has thoroughly covered the problems both of the patient and of her disease. She was first seen in this hospital by a student from our third-year class. She was the student's first patient. You can imagine what an impression it has made on him. Our thoughts were much as Dr. Berg's. So far as I know polycythemia vera is not seen in a twenty-four-year-old woman. When we found the bruit at the left apex, we thought we were dealing with an arteriovenous fistula and requested x-ray films with that in mind. The interesting thing to me was the psychologic symptoms. I had her seen both before and after operation by Dr. Quarton, of the Department of Psychiatry. I saw the patient a month after operation. She was fine. She was pink instead of magenta, she looked very well, and she told me that many of her symptoms had disappeared. The hematocrit was 50 per cent, the red-cell count was 5,100,000, and the hemoglobin was 15 gm. per 100 cc.

DR. BLAND: And the clubbed fingers?

DR. STANBURY: They were never striking.

DR. GARDNER C. QUARTON: I was very much interested in the patient's muddleheadedness. I believed preoperatively that it was related to depression and her emotional problems and not primarily to the disease. She has done very well postoperatively, but I still hold the same opinion. I think she will have further symptoms of an emotional type.

A PHYSICIAN: Could she have had arteriovenous aneurysms in her brain to account for the cerebral symptoms?

DR. CASTLEMAN: I have not seen a case report of a pulmonary arteriovenous shunt associated with one of the same sort in the brain.

DR. STANBURY: We considered that. She had a normal electroencephalogram, and had no bruit over the skull.

DR. BAUER: Do they ever occur?

DR. HANELIN: Those in the brain are not associated with polycythemia; they are relatively common malformations, usually with arteriovenous communications.

DR. BERG: The shunt is from left to right in that case.

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VIEWS ON MEDICAL PRACTICE

DESPITE some reluctance on the part of the Old Guard that dies but never surrenders, various mechanisms of practice are being tried out in order that the progress medicine has made may be utilized to its utmost without abandoning the personal factor in medical relations or bankrupting that eventual recipient of all that is good and bad in the changing tides of medical progress, the patient. This is often a triangular problem that involves the hospital as well as the doctor and the patient.

In recognizing the hospital as implicated in the problem, the kind of hospital must also be considered, three types in particular being essential to the discussion. The community hospital, of the three, is vitally useful at its intimate level of functioning and is closest to the family practice of medicine. Next comes the large, usually privately supported or voluntary hospital, so-called, above the community level but also devoted mainly to the care of patients. At the peak is the teaching hospital, however supported, in which the care of the patient must be combined with the teaching of students and a research program.

The responsibilities of the hospital in the changing order have been difficult both to define and to establish. They are, of course, primarily to the patient, but there is also a mutual responsibility between doctor and hospital — between staff and board — that has often been ignored or allowed to deteriorate. For medical care must be a co-operative community project, which hospital administration and physician alike must recognize as such.

The hospital at the community level gives its broadest service with an open staff, membership on which is determined only by minimum acceptable professional and ethical standards. Board certification and membership in special societies should certainly not be a requirement for staff appointment although limited responsibilities only should be permitted before the physician's qualifications are proved; the capabilities of those who have not sought such certification or membership should be diligently appraised.

Medical care is now offered to the paying public under four general systems of practice. Private physician-sponsored groups provide efficiency and ease of consultation, control of total cost, a single bill based presumably on the ability of the patient to pay, and a unit-record. Their disadvantages lie in their restricted sphere of consultation and too great a dispersal of responsibility.

Lay-sponsored groups provide in principle about the same advantages as physician-sponsored groups, but the disadvantages are increased. Commercialism and competitive selling of services is liable to develop and bring about a deterioration in the quality of care.

The hospital-physician-sponsored group offers, in the opinion of many, the best solution to the problem of medical care. The fees are paid to the hos-

pital, which in turn pays the members according to a carefully determined schedule. The organization of such a group must protect any of the contracting agents — hospital, physician and patient — from exploitation by any of the others.

Individual private practice, still the most important method of delivering medical care, has the advantages of complete independence and direct personal responsibility. Some of the best and some of the worst medical service is delivered through this historic channel. It should and will continue, but some form or forms of group effort are necessary to complement it, and probably in many circumstances offer the most for the money.

MEETING OF THE HOUSE OF DELEGATES

One of the more controversial matters brought before the House of Delegates of the American Medical Association at its June meeting was the report of the Committee for the Study of Relations between Osteopathy and Medicine.

Some of the better colleges of osteopathy, in an effort to improve their instruction in medicine, have invited qualified internists and other well-trained physicians to conduct courses in their schools. Section 1 of Chapter II of the *Principles of Medical Ethics* of the American Medical Association flatly states, however, "All voluntarily associated activities with cultists are unethical."

The Committee, believing that "pursuant to the objectives and responsibilities of the American Medical Association, which are to improve the health and medical care of the American people, it is the policy of the Association to encourage improvement in the undergraduate and postgraduate education of doctors of osteopathy," recommended that the House of Delegates go on record as declaring that "so little of the original concept of osteopathy remains that it does not classify medicine as currently taught in schools of osteopathy as the teaching of 'cultist' healing." The House of Delegates did not accept this recommendation, but preferred to postpone action for another year.

Many of the delegates apparently believed that the implication of this recommendation, even though not stated in so many words, was that to make it proper for ethical physicians to teach in osteopathic schools, osteopaths are not to be considered "cultists" while they are being taught medicine by physicians.

The Committee for the Study of Relations between Osteopathy and Medicine did not recommend any change in the principle of ethics involved, but preferred to designate certain osteopathic activities as noncultist.

In Massachusetts osteopaths are legally licensed to practice either osteopathy or medicine. They may be and are associated with by eminently respectable "regular" physicians and surgeons whenever they ask assistance for the benefit of a sick patient. An ethical surgeon should not be compelled to refuse to operate on the patient of any practitioner, if that patient urgently requires his help.

Homeopathy was once a cult. Osteopathy began as a cult, and may still be so practiced in many localities. It is confidently expected that in due time, as osteopathic physicians and the general public become more familiar with the demonstrated truths of contemporary medical science, common sense will lead them to modify, or even to abandon theories and principles that do not withstand the test of controlled observation.

It may be unwise to base any action upon a redefinition of certain activities of the osteopaths as "cultist" and others as noncultist. A simple qualifying clause to the effect that physicians of the orthodox school may "associate" with any type of practitioner if such association is necessary for the health of a patient or in the public interest would offer a more intelligent solution to the problem.

WHO: SIXTH GENERAL ASSEMBLY

The World Health Organization is in generally sound financial condition, Milton P. Siegel, assistant director-general in charge of the Division of Administration and Finance, reported at the Sixth World Health Assembly in Geneva in May.

A serious situation has arisen in financing the expanded Technical Assistance Program for 1953, however. The goal of $25,000,000 set by the United Nations General Assembly was still $4,000,000

short when all the chips were in and the countries participating in the program had announced their pledges in February. Despite financial assistance from UNICEF and the transfer of certain projects to the regular WHO program and the Pan American Sanitary Bureau, various new Technical Assistance and other activities will have to be postponed.

Nepal, on recommendation of the Committee on Administration, Finance and Legal Matters, was accepted as the eightieth full member of the organization, further evidence that it is possible for nations of good will to unite in a common cause. The Committee also recommended acceptance of the Philippine proposal that would enable the Republic of China to resume active participation in the Organization.

Diseases of the Liver. — *The fact that a single organ may be subject to a catalogue of diseases, the description and treatment of which fills a tome of 468 pages, octavo, impresses the student with the frailty of humanity in its physical organization.*

Boston M. & S. J. *July 27, 1853*

MASSACHUSETTS MEDICAL SOCIETY

ROBERT L. DeNORMANDIE
1876–1953

The long and distinguished life of an obstetrician and public servant ended on April 20, when Dr. Robert Laurent DeNormandie died suddenly of a cardiac accident at Woodstock, Vermont.

Dr. DeNormandie was born in Portsmouth, New Hampshire, on August 24, 1876. His father, James DeNormandie, was a Unitarian minister whose Calvinist forebears had emigrated from Switzerland to Pennsylvania in 1707. His mother was Emily Farnum Jones, who stemmed from an old New Hampshire family. In 1894 Dr. DeNormandie graduated from the Roxbury Latin School, and in the following fall he entered Harvard College with the Class of 1898. In 1902 he graduated from Harvard Medical School. He was a house officer on the South Surgical Service at the Massachusetts General Hospital from 1902 to 1903 and then an intern at the Boston Lying-in Hospital when it was still on McLean Street. Upon completion of that appointment he became a member of the Staff and entered upon his professional career as an obstetrician, from which he did not retire until 1946.

There were one or two doubtful moments during his student days that he often recalled with humor and some chagrin. He was not a scholar while at school, and the headmaster refused to recommend him to Harvard College. His subsequent success both at college and in medical school afforded him considerable amusement and satisfaction.

Near the end of his service as a house officer at the Massachusetts General Hospital he was summarily dismissed by Dr. Washburn (recently returned from military service in the Spanish War) because of an unusually noisy and tempestuous evening party held by the House Staff. Dr. DeNormandie was the senior house officer on duty that night and, although he was able to prove that he had been asleep and ignorant of the whole affair, because he was the senior officer on duty he was held responsible for the incident. Along with one or two of the participants he was not allowed to complete his service.

At the time of his dismissal from the Massachusetts General Hospital he had already been intern to the Lying-in Hospital. Rumor of his dismissal from the Massachusetts General Hospital spread along McLean Street, and his appointment was withdrawn. Dr. William Richardson, professor of obstetrics at that time, came to his rescue, and although Washburn remained adamant Dr. Richardson readily convinced the authorities of the Lying-in Hospital that Dr. DeNormandie should be reinstated.

The first years after joining the staff of the Boston Lying-in Hospital were devoted to the teaching and practice of obstetrics, and at the request of Dr. Richard Cabot he wrote the book on obstetrics in the case-history series for medical teaching.

During World War I he went to France for the Red Cross to aid the French with obstetrics. He also served with the Boston medical group that went in 1917 to Halifax to aid the victims of the munitions disaster.

In 1924 he was asked to assume the chairmanship of a committee to study maternal and infant mortality for the Children's Bureau in Washington. The report of this committee, published as a monograph in 1928, has been considered a milestone in understanding of the public-health aspects of maternal and infant mortality. He continued to serve as a consultant to the Children's Bureau through the Hoover Administration and for the first twelve years of the New Deal.

During this period he became increasingly interested in the problems of the Massachusetts Medical Society and for twelve years served on the Committee on Ethics and Discipline, for the last three as chairman. In 1934-1936 he was president of Suffolk District Medical Society. For twenty years he

served the town of Lincoln as chairman of the Board of Health.

As insurance schemes such as the Blue Cross developed it was natural to find Dr. DeNormandie at the forefront. He was one of the original five medical trustees of the White Cross, a nonprofit insurance plan for comprehensive medical care launched in 1941. This plan, like the Blue Cross and the Public Health clinics, was opposed at the time by organized medicine as too revolutionary, but that he was a part of it was typical of his whole life.

Leverett Saltonstall, while governor, appointed him to the Board of Trustees of Tewksbury State Hospital. Elected to the chairmanship of the Board he continued to serve in that capacity till the time of his death, demanding untiring, humane care of the sick and unhesitatingly dismissing those he considered in any way professionally incompetent. He was as warm and thoughtful and worried about the patients of the State Hospital as he had been about each of his own private patients.

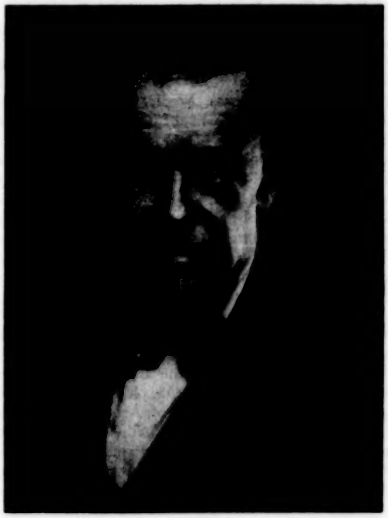
He married Alice Woodward Brown on April 18, 1906. They had three children, James, Alice and Ellen, all of whom are married and, with Mrs. DeNormandie, survive him. Two days before his death, he and Mrs. DeNormandie celebrated their forty-seventh wedding anniversary. Throughout his professional life, Mrs. DeNormandie constantly encouraged him in his work and interests, particularly at the times when his concepts of the needs of preventive medicine were most under criticism.

O. C.

REGINALD FITZ
1885-1953

All sons do not follow happily along the trail set by their distinguished fathers. Sometimes the sons are so like their fathers that there is not room for two strong personalities in the same office, in the same field or in the same profession. Fortunately this was not so with Reginald Heber Fitz and Reginald Fitz. The younger Fitz inherited his father's intellectual ability, but this ability took a very different form. The elder Fitz acquired fame in his reconstruction of clinical appendicitis from autopsy material. Shortly thereafter, in his Goulstonian Lectures, whose content fifty years later is still monumental and standard, he established pancreatitis as an entity. The elder Fitz, as Hersey Professor of the Theory and Practice of Physic at Harvard Medical School, insisted on logic as a necessary factor in clinical diagnosis.

The younger Fitz, more impetuous and more ardent than his father, even if less relentless, made as his early goal the acquisition of all medical knowledge. Of course, he knew that Henry J. Bigelow was reported to be the last man in Boston — at Harvard Medical School and at the Massachusetts General Hospital — who had any claims to know all of medicine. Born in 1885, Reginald Fitz graduated from Harvard College in 1906 and from Harvard Medical School in 1909, serving his medical internship at the Massachusetts General Hospital, 1909-1911. It was characteristic that from 1911 to 1933 he was volunteer assistant to Dr. William Sydney Thayer at the Johns Hopkins Hospital in Baltimore. After the Peter Bent Brigham



REGINALD FITZ

Hospital opened in Boston, Fitz became assistant resident from 1913-1915. But the lure of new pastures found him assistant resident physician at the Rockefeller Hospital, New York City, 1915-1917. In World War I he served with the Harvard Unit in France, entering as captain and shortly afterward becoming major and head of the Medical Service. On June 29, 1918, at Sir William Osler's home in Oxford, England, Fitz was married to Phoebe Wright, a daughter of a Canadian physician and one of a goodly number of Canadians who called Sir William Osler "Uncle William."

After the War, Fitz, still idealistic, impetuous and insatiable, was on the staff of the Mayo Clinic from 1920 to 1922. He returned to Boston in 1922 and became consulting physician to the Peter Bent Brigham Hospital and associate professor of medicine at Harvard Medical School from 1922 to

1936. For four years, 1936 to 1940, he was Wade Professor of Medicine, Boston University School of Medicine and director of the Evans Memorial, Massachusetts Memorial Hospitals.

By this time, Fitz's interests were centered mainly on historical medicine, as shown by his bibliography of 180 titles. His early publications were largely concerned with nephritis and diabetes. The later writings reflected his scholarly mind. He became a lecturer on the history of medicine and assistant dean at Harvard Medical School and Harvard University Marshal. He helped build the Library of the Medical School into a useful if small collection. He was energetic, even if a bit predatory, about finding a sanctum in that library for some of his colleagues' prized books and other precious mementos. At the same time, he was active as a trustee of the Boston Medical Library and consultant to the Army Medical Library in Washington. He was also a trustee of the Brookline Public Library. He was president of the Suffolk Medical Society, 1938-1940, president of the Massachusetts Medical Society, 1945-1948, and president of the American College of Physicians, 1949-1950 (he was made a master of the American College of Physicians in 1953). He was chairman of the Medical Advisory Board of No. 13 Selective Service, Boston, 1940-1947.

In addition to many committees of which he was always an active and useful member, he was a trustee of Wellesley College, and a trustee of the Perkins Institute for the Blind and president of the Board from 1946-1953. He was a member of the American Academy of Arts and Sciences. His was a very valuable life, filled with unselfish activities, a life of gentle and solicitous devotion to his family, his friends, to medicine, to his associates and to the many whom he did not know and who did not know him but who are in his debt. He lived courageously and busily on borrowed time for two years until his death, May 27, 1953.

R.I.L.

CORRESPONDENCE

REVOCATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held June 25, 1953, it was voted to revoke the registration of Dr. Jacob Aronson, 64 Garden Road, Brookline, Massachusetts.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

RESTORATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held June 25, 1953, it was voted to restore the registration of Dr. Jackson M. Rice, of Hyannis, Massachusetts.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

History of the Royal Medical Society, 1737-1937. By James Gray, M.A., F.R.S.E. Edited by Douglas Guthrie, M.D., F.R.C.S.E., lecturer in history and medicine, University of Edinburgh. With a foreword by Sir Robert Hutchison, Bart., M.D. LL.D., F.R.C.P. 8°, cloth, 355 pp., with illustrations. Edinburgh: University Press, 1952. 42/-

A History of Science: Ancient science through the golden age of Greece. By George Sarton, Sc.D., Ph.D., LL.D. 8°, cloth, 646 pp., with 101 illustrations. Cambridge: Harvard University Press, 1952. $10.00.

Die Nachkommen geisteskranker Elternpaare: Der Einfluss endogener Elternpsychosen auf die Psychosen, Charaktere und Lebensschicksale ihrer Kinder. By Prof. Dr. Med. Günter Elsässer, provisional medical councilor, Landesheilanstalt Bonn. 8°, cloth, 340 pp., with 38 genealogical tables. Stuttgart: Georg Thieme, 1952. Ganzleinen DM 33.-(Distributed by Grune and Stratton, New York.)

NOTICES

AMERICAN ACADEMY OF DENTAL MEDICINE

The mid-winter meeting of the American Academy of Dental Medicine will be held on Sunday, December 6, in the Hotel Statler, New York City. The theme of the scientific session will be geriatrics.

All interested persons are cordially invited. Further details of the program may be obtained from the National Secretary, Dr. William M. Greenhut, 124 East 84th Street, New York 28, New York.

INTER-SOCIETY CYTOLOGY COUNCIL

The first annual meeting of the Inter-Society Cytology Council will be held in Philadelphia on November 19 and 20. Those interested in presenting papers pertaining to the cytologic method for the diagnosis of cancer and related subjects are urged to send titles (and abstracts not over 300 words in length) before August 1 to the Chairman of the Program Committee, Dr. A. E. Rakoff, Jefferson Medical College, 1025 Walnut Street, Philadelphia 3, Pennsylvania.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

Applications for certification by the American Board of Obstetrics and Gynecology for the 1954 Part I examinations are now being accepted. Candidates are urged to make such application during July or August.

All candidates are required to submit with their application a plain typewritten list of all patients admitted to the hospitals where they practice for the year preceding their application or the year before their request for re-opening of their application, with the diagnosis, pathological diagnosis, nature of treatment and end result.

Attention of all candidates is called to a change in date. Application for examination or re-examination and requests for resubmission of case abstracts must be made to the Secretary before October 1.

All requests should be made to Robert L. Faulkner, M. D., Secretary, American Board of Obstetrics and Gynecology, 2105 Adelbert Road, Cleveland 6, Ohio. A large, stamped, self-addressed envelope should be included.

SEVENTH INTERNATIONAL CONGRESS OF PEDIATRICS

The Seventh International Congress of Pediatrics will be held in Havana, Cuba, October 12 to 17.

(Notices concluded on page xvii)